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PUBLIC COMMENTS

ÉBAUCHE POUR
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Canadian Environmental Protection Act, 1999

PRIORITY SUBSTANCES LIST

ASSESSMENT REPORTS

2-METHOXYETHANOL

2-ETHOXYETHANOL

2-BUTOXYETHANOL

Environment Canada
Health Canada

August 2000

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2-METHOXYETHANOL ASSESSMENT REPORT

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LIST OF ACRONYMS AND ABBREVIATIONS

BCF	bioconcentration factor
CAS	Chemical Abstracts Service
CEPA	*Canadian Environmental Protection Act*
CEPA 1999	*Canadian Environmental Protection Act, 1999*
CFC	chlorofluorocarbon
CI	confidence interval
CTV	Critical Toxicity Value
EEV	Estimated Exposure Value
ENEV	Estimated No-Effects Value
GWP	Global Warming Potential
HC_5	hazardous concentration to 5% of test species
K_{ow}	octanol/water partition coefficient
kg-bw	kilogram body weight
LC_{50}	median lethal concentration
LD_{50}	median lethal dose
LOEL	Lowest-Observed-Effect Level
MAA	methoxyacetic acid
MALD	methoxyacetaldehyde
NOEL	No-Observed-Effect Level
ODP	Ozone Depletion Potential
POCP	Photochemical Ozone Creation Potential
PSL	Priority Substances List
RR	relative risk

Synopsis

2-Methoxyethanol is not commercially produced in Canada. It is imported for use mainly as a chemical processing aid and as a component of formulated products. The use of 2-methoxyethanol has declined over the past few years because it has been partially replaced in some countries by other substances. All reported environmental releases are to the atmosphere.

2-Methoxyethanol reacts with hydroxyl radicals in the air with a half-life of about 18 hours. Much of the 2-methoxyethanol released to the atmosphere is predicted to remain in air, but a substantial proportion would partition to water and to soil. 2-Methoxyethanol is biodegraded in surface water and aerobic soil with an estimated half-life of 1–4 weeks. It is somewhat more persistent under aerobic conditions. 2-Methoxyethanol has a very low octanol/water partition coefficient and is therefore not expected to bioaccumulate to any significant degree. There are very few available data on concentrations of 2-methoxyethanol in the environment in Canada or elsewhere.

Data on toxicity exist for aquatic organisms, including microorganisms, invertebrates and fish. 2-Methoxyethanol is not very toxic to these organisms; in a number of studies, the LC_{50} was above the highest concentration tested.

Because of the paucity of environmental monitoring data, exposure values for the environmental assessment were estimated based on modelling. Estimated environmental concentrations of 2-methoxyethanol are several orders of magnitude lower than the adverse effects thresholds calculated for sensitive organisms.

2-Methoxyethanol is not involved in stratospheric ozone depletion and is not an important contributor to climate change or ground-level ozone formation.

Based on a relatively extensive database in experimental animals, 2-methoxyethanol has consistently been associated with a wide range of adverse effects on health, including those considered to be severe and irreversible (e.g., teratogenicity), with some occurring at relatively low levels of exposure. However, although relevant data are limited, exposure of the general population through environmental media is expected to be small, due to reported declining use of the compound in recent years as it is replaced with less hazardous compounds. Margins between worst-case estimates of exposure from environmental media and lowest effect levels for developmental toxicity obtained in toxicological investigations in experimental animals are large. However, available data are insufficient to conclude that margins between worst-case estimates of exposure in consumer products and lowest effect levels are adequate.

Based on these considerations, it is concluded that 2-methoxyethanol is not entering the environment in a quantity or concentration or under conditions that have or may have an

immediate or long-term harmful effect on the environment or its biological diversity or that constitute or may constitute a danger to the environment on which life depends. On the basis principally of its high health hazard potential, 2-methoxyethanol may be entering the environment in a quantity or concentration or under conditions that constitute or may constitute a danger in Canada to human life or health. Therefore, it is proposed that 2-methoxyethanol be considered "toxic" under Paragraph 64(c) of the *Canadian Environmental Protection Act, 1999* (CEPA 1999).

It is recommended that additional information be acquired on patterns of use of 2-methoxyethanol in Canada, particularly in relation to its presence in consumer products. It is further recommended that, in view of the profile of toxicity of 2-methoxyethanol, potential for exposure of the general population to this compound be eliminated or reduced to the extent possible.

1.0 INTRODUCTION

The *Canadian Environmental Protection Act, 1999* (CEPA 1999) requires the federal Ministers of the Environment and of Health to prepare and publish a Priority Substances List (PSL) that identifies substances, including chemicals, groups of chemicals, effluents and wastes, that may be harmful to the environment or constitute a danger to human health. The Act also requires both Ministers to assess these substances and determine whether they are "toxic" as defined in Section 64 of the Act, which states:

> ...a substance is toxic if it is entering or may enter the environment in a quantity or concentration or under conditions that
> (a) have or may have an immediate or long-term harmful effect on the environment or its biological diversity;
> (b) constitute or may constitute a danger to the environment on which life depends; or
> (c) constitute or that may constitute a danger in Canada to human life or health.

Substances that are assessed as "toxic" as defined in Section 64 may be placed on Schedule I of the Act and considered for possible risk management measures, such as regulations, guidelines, pollution prevention plans or codes of practice to control any aspect of their life cycle, from the research and development stage through manufacture, use, storage, transport and ultimate disposal.

Based on initial screening of readily accessible information, the rationale for assessing 2-methoxyethanol (along with 2-ethoxyethanol and 2-butoxyethanol) provided by the Ministers' Expert Advisory Panel on the Second Priority Substances List (Ministers' Expert Advisory Panel, 1995) was as follows:

> Potential sources of exposure to these compounds include releases from various industrial and consumer uses. These compounds are widely used as solvents in paints and protective coatings; in printing inks, industrial solvents and cleaners; in the production of plasticizers; as a de-icer in fuels and automotive brake fluids; and in electronics manufacturing. Effects due to exposure include disorders of the central nervous system, blood system, kidneys and liver in both humans and animals. An assessment is required to determine the presence of these substances in the Canadian environment, exposure and the potential risks to human health.

Descriptions of the approaches to assessment of the effects of Priority Substances on the environment and human health are available in published companion documents. The document entitled "Environmental Assessments of Priority Substances under the *Canadian Environmental Protection Act*. Guidance Manual Version 1.0 — March 1997" (Environment Canada, 1997a) provides guidance for conducting environmental assessments of Priority Substances in Canada. This document may be purchased from:

Environmental Protection Publications
Environmental Technology Advancement Directorate
Environment Canada
Ottawa, Ontario
K1A 0H3

It is also available on the Internet at www.ec.gc.ca/cceb1/eng/psap.htm under the heading "Technical Guidance Manual." It should also be noted that the approach outlined therein has evolved to incorporate recent developments in risk assessment methodology, which will be addressed in future releases of the guidance manual for environmental assessments of Priority Substances.

The search strategies employed in the identification of data relevant to the assessment of entry, environmental fate and exposure and potential effects on the environment (prior to October 1999) are presented in Appendix A. Review articles were consulted where appropriate. However, all original studies that form the basis for determining whether 2-methoxyethanol is "toxic" under Paragraph 64(a) or 64(b) of CEPA 1999 have been critically evaluated by staff of Environment Canada.

The approach to assessment of effects on human health is outlined in the following publication of the Environmental Health Directorate of Health Canada: "*Canadian Environmental Protection Act* — Human Health Risk Assessment for Priority Substances" (Health Canada, 1994), copies of which are available from:

Environmental Health Centre
Room 104
Health Canada
Tunney's Pasture
Ottawa, Ontario
K1A 0L2

or on the Environmental Health Directorate publications web site (www.hc-sc.gc.ca/ehp/ehd/catalogue/bch.htm). The approach is also described in an article published in the *Journal of Environmental Science and Health — Environmental Carcinogenesis & Ecotoxicology Reviews* (Meek *et al*., 1994). It should be noted that the approach outlined therein has evolved to incorporate recent developments in risk assessment methodology, which are described on the Environmental Substances Division web site (www.hc-sc.gc.ca/ehp/ehd/bch/env_contaminants/psap/psap.htm) and which will be addressed in future releases of the approach paper for the assessment of effects on human health.

The approach to assessment of 2-methoxyethanol is necessarily restricted because of the extremely limited data upon which to base estimates of population exposure. Moreover, use of this substance has declined substantially worldwide in recent years, as it has been replaced with less hazardous substances. Indeed, available information indicates that 2-methoxyethanol has not been produced in Canada in the last several years. Therefore, in view of the fact that measures have been introduced to reduce population exposure, a screening approach has been adopted for assessment of whether or not the substance would be considered "toxic" under Paragraph 64(c) of CEPA 1999 primarily as a basis for determining whether current measures are sufficiently protective of human health.

In view of the limited objectives of this screening assessment, therefore, lowest effect levels identified primarily from secondary sources are compared with worst-case or bounding estimates of exposure. The adequacy of these rather crude margins of exposure is considered in relation to intake from various sources estimated on the basis of primary review of the limited available Canadian data on exposure from various sources, including environmental media and consumer products. On this basis, areas where additional information may be required to ensure that current measures for reduction of population exposure are sufficiently protective have been identified.

Data on the health effects of 2-methoxyethanol were identified primarily from a review prepared in 1996 by BIBRA International, which was updated and modified in 1998 (BIBRA International, 1996/Health Canada, 1998). Relevant data identified subsequent to this update are summarized in Health Canada (1999). The search strategies used in the identification of relevant data on health effects from 1996 to October 1999 are outlined in Appendix A.

Sections of the Assessment Report related to the environmental assessment of 2-methoxyethanol and the environmental Supporting Document (Environment Canada, 1999) were prepared or reviewed by the members of the Environmental Resource Group, established by Environment Canada to support the environmental assessment:

D. Boersma, Environment Canada
R. Breton, Environment Canada
P. Cureton, Environment Canada
N. Davidson, Environment Canada
R. Desjardins, Environment Canada
L. Hamel, Union Carbide Canada Inc.
B. Lee, Environment Canada
S. Lewis, Chemical Manufacturers' Association
B. Sebastien, Environment Canada
K. Taylor, Environment Canada (lead for the environmental assessment)

Sections of the Assessment Report relevant to the environmental assessment and the environmental Supporting Document (Environment Canada, 1999) were also reviewed by:

S. Dobson, Institute of Terrestrial Ecology
C. Staples, Assessment Technologies Inc.

The health-related sections of the Assessment Report were prepared and the background Supporting Document was updated by the following staff of Health Canada:

H. Hirtle
K. Hughes
M.E. Meek
L. Turner

Adequacy of data coverage and defensibility of the conclusions presented in this health assessment were considered in a written review by:

M. Dourson, TERA
J.B. Knaak, Oxychem (retired)
R.A. Rudel, Silent Spring Institute

The health-related sections of the Assessment Report were reviewed and approved by the Health Protection Branch Risk Management meeting of Health Canada.

The entire Assessment Report was reviewed and approved by the Environment Canada/Health Canada CEPA Management Committee.

The text of the Assessment Report has been structured to address environmental effects initially (relevant to determination of "toxic" under Paragraphs 64(a) and (b)), followed by effects on human health (relevant to determination of "toxic" under Paragraph 64(c)).

Copies of this Assessment Report are available upon request from:

Inquiry Centre
Environment Canada
Main Floor, Place Vincent Massey
351 St. Joseph Blvd.
Hull, Quebec
K1A 0H3

or on the Internet at:

www.ec.gc.ca/cceb1/eng/public/index_e.html

Unpublished supporting documentation, which presents additional information, is available upon request from:

Commercial Chemicals Evaluation Branch
Environment Canada
14th Floor, Place Vincent Massey
351 St. Joseph Blvd.
Hull, Quebec
K1A 0H3

or

Environmental Health Centre
Room 104
Health Canada
Tunney's Pasture
Ottawa, Ontario
K1A 0L2

2.0 SUMMARY OF INFORMATION CRITICAL TO ASSESSMENT OF "TOXIC" UNDER CEPA 1999

2.1 Identity and physical/chemical properties[1]

2-Methoxyethanol has the empirical molecular formula $C_3H_8O_2$, the structural formula $CH_3OCH_2CH_2OH$ and a molecular weight of 76.1 g/mol. Its Chemical Abstracts Service (CAS) registry number is 109-86-4. 2-Methoxyethanol is a colourless viscous liquid with a water solubility of 500 000 mg/L (DMER and AEL, 1996), an octanol/water partition coefficient (log K_{ow}) of –0.77 (Hansch and Leo, 1985), a vapour pressure of 1300 Pa at 25°C (Riddick *et al.*, 1986) and a Henry's law constant of 0.198 $Pa \cdot m^3/mol$ (calculated value) (DMER and AEL, 1996). The conversion factor for 2-methoxyethanol in air is 1 ppm = 3.11 mg/m^3.

2-Methoxyethanol is a substance in the class of chemicals sometimes referred to as "glycol ethers."

Synonyms for 2-methoxyethanol include 2-methoxy-1-ethanol, ethylene glycol monomethyl ether and methyl Cellosolve.

2.2 Entry characterization

2.2.1 Production, importation and uses

2-Methoxyethanol was not produced in or exported from Canada in 1995 and 1996, according to data submitted to Environment Canada by 10 companies in a survey conducted under the authority of Section 16 of CEPA (Environment Canada, 1997b). According to data reported through this survey, importation of 2-methoxyethanol totalled 1016 tonnes in 1995 and 486 tonnes in 1996.

2-Methoxyethanol has been reported to be used in paints, coatings, inks, cleaners, polishes, brake fluids and jet fuels and to find wide application as a solvent, chemical intermediate and solvent coupler of mixtures and water-based formulations (Stemmler *et al.*, 1997). Data submitted to Environment Canada in the survey conducted under the authority of Section 16 of CEPA indicated that 104 and 34 tonnes of 2-methoxyethanol were used in Canada in 1995 and 1996, respectively, mainly as a chemical processing aid and as a component of formulated products (Environment Canada, 1997b). The use of 2-methoxyethanol has declined over the past few years because it has been partially replaced in some countries by other substances.

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[1] See the environmental Supporting Document (Environment Canada, 1999) for a more complete listing of ranges of values reported and criteria for selection of physical and chemical properties.

According to monitoring data on concentrations in occupational air collected between 1983 and 1994 by the Ontario Ministry of Labour (Rachamin *et al*., 1996), the majority of industries with concentrations of 2-methoxyethanol above the limit of detection were commercial printing and small electrical appliances, machinery and equipment manufacturing.

2.2.2 Sources and releases

2.2.2.1 Natural sources

2-Methoxyethanol has not been reported to occur as a natural product (U.S. EPA, 1986; WHO, 1990). There are no known reactions that would lead to the *in situ* production of 2-methoxyethanol or other glycol ethers in the atmosphere (Rogozen *et al*., 1987).

2.2.2.2 Anthropogenic sources

Total on-site environmental releases of 2-methoxyethanol reported to the National Pollutant Release Inventory in 1994 amounted to 17.0 tonnes (NPRI, 1996). All of this was released into the atmosphere from one facility in southern Ontario. Total transfers of 2-methoxyethanol for off-site disposal amounted to 2.12 tonnes in 1994, with all going to incinerators. A reported total of 0.07 tonnes of 2-methoxyethanol was sent for energy recovery in 1994 (NPRI, 1996).

In 1995, total on-site environmental releases of 2-methoxyethanol reported to the National Pollutant Release Inventory amounted to 6.3 tonnes (NPRI, 1998). All of this was released to the atmosphere from stack emissions at one facility in southern Ontario. Total transfers of 2-methoxyethanol for off-site disposal amounted to 33.9 tonnes in 1995 (NPRI, 1998). No releases of 2-methoxyethanol were reported to the National Pollutant Release Inventory in 1996 (NPRI, 1998).

According to data submitted in the CEPA Section 16 survey (with different reporting requirements from the National Pollutant Release Inventory), environmental releases of 2-methoxyethanol in Canada totalled 8.7 tonnes in 1996, all to the air (Environment Canada, 1997b).

The Canadian Chemical Producers' Association (1997) reported total emissions of 2-methoxyethanol of 3.0, 0.036, 0.02 and 0.009 tonnes from member companies in 1992, 1993, 1994 and 1995, respectively, all of which were released to air by a single company. Reported releases totalled 0.006 tonnes in 1996, 0 tonnes in 1997 (Canadian Chemical Producers' Association, 1999a) and 0 tonnes in 1998 (Canadian Chemical Producers' Association, 1999b).

2.3 Exposure characterization

2.3.1 Environmental fate

2.3.1.1 Air

Due to its high volatility (vapour pressure 1300 Pa at 25°C), 2-methoxyethanol is expected to be present principally in air. Howard *et al.* (1991) calculated a half-life in the range of 5.7–57 hours for 2-methoxyethanol in the atmosphere, based on the rate constant for its reaction with hydroxyl radicals. The U.S. Environmental Protection Agency (U.S. EPA, 1986) calculated a half-life of 17.5 hours for the reaction of 2-methoxyethanol with atmospheric hydroxyl radicals, assuming an ambient concentration of hydroxyl radicals of 8.0×10^5 molecules/cm^3.

2.3.1.2 Surface water

2-Methoxyethanol volatilizes rapidly from the water surface, with an estimated half-life of 2.8 hours (Lyman *et al.*, 1982).

Biodegradation of 2-methoxyethanol in natural water would also be significant (U.S. EPA, 1986). Howard *et al.* (1991) estimated a half-life in water of 1–4 weeks, based on unacclimated aerobic biodegradation.

2.3.1.3 Groundwater

Howard *et al.* (1991) estimated a half-life in groundwater of 2–8 weeks, based on unacclimated aerobic biodegradation.

2.3.1.4 Soils

2-Methoxyethanol would be expected to be highly mobile in soil because of its high water solubility and low K_{ow} (U.S. EPA, 1986), but much of the substance would volatilize from the soil surface.

Howard *et al.* (1991) estimated a half-life in aerobic soils of 1–4 weeks, based on unacclimated aerobic biodegradation. 2-Methoxyethanol underwent biooxidation to 2-methoxyacetic acid (MAA) by the soil bacterium *Alcaligenes* MC11, which was able to use 2-methoxyethanol as a source of carbon (Harada and Nagashima, 1975). *Pseudomonas* sp. 4-5-3, *Xanthobacter autotrophicus* EC1-2-1 and a bacterium identified only as "strain MC2-2-1" could also use 2-methoxyethanol as a source of carbon for aerobic growth (Kawai, 1995).

For anaerobic soils, Howard *et al.* (1991) estimated an anaerobic half-life in soil of 4–16 weeks for 2-methoxyethanol, based on its unacclimated aqueous aerobic biodegradation half-life.

2.3.1.5 Biota

A bioconcentration factor (BCF) of 0.15 was estimated for 2-methoxyethanol, based on its log K_{ow} of –0.77 and using the equation proposed by Lyman *et al.* (1982): log BCF = 0.76 log K_{ow} – 0.23 (U.S. EPA, 1986). Bioaccumulation of 2-methoxyethanol in aquatic organisms would therefore not be significant.

2.3.1.6 Environmental distribution

Because of the high water solubility and low log K_{ow} of 2-methoxyethanol, physical adsorption to suspended solids and sediments should not be significant (U.S. EPA, 1986). Based on its physical/chemical properties, 2-methoxyethanol is expected to volatilize from soil or leach rapidly into the ground (Howard, 1990).

The environmental partitioning of 2-methoxyethanol when released into air, water or soil was estimated by a Level III fugacity model (DMER and AEL, 1996). Values for input parameters were as follows: molecular weight, 76.1 g/mol; vapour pressure, 1300 Pa; water solubility, 500 000 mg/L; log K_{ow}, –0.77; Henry's law constant, 0.198 Pa·m^3/mol; half-life[2] in air, 55 hours; half-life in water, 550 hours; half-life in soil, 550 hours; and half-life in sediment, 1700 hours. Modelling was based upon an assumed emission rate of 1000 kg/hour, although the emission rate used would not affect the estimated percent distribution. If 2-methoxyethanol is emitted into air, EQC (Equilibrium Criterion) fugacity Level III modelling predicts that about 50% would be present in air, while approximately 25% would be present in soil and about 25% in water. If 2-methoxyethanol is emitted into water, more than 99% would be present in water. If 2-methoxyethanol is released to soil, about 75% would be present in the soil, while approximately 25% would be present in water (DMER and AEL, 1996).

2.3.2 Environmental concentrations

Very few data on levels of 2-methoxyethanol in the environment have been identified for Canada or elsewhere (U.S. EPA, 1986; WHO, 1990). One study was conducted to determine concentrations of 2-methoxyethanol in multiple Canadian media to which humans are exposed, including drinking water and indoor and outdoor air (Conor Pacific Environmental Technologies, 1998), as outlined below in Section 2.3.2.1. Additional data on levels of 2-methoxyethanol in specific media are presented in the subsequent sections.

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[2] For each environmental compartment, DMER and AEL (1996) use a series of ranges of half-life times (<10 hours, 10–30 hours, 30–100 hours, etc.), and the half-life of the particular substance is assigned to the appropriate range, based on a consideration of available persistence data. The geometric mean of this range is then used as an input parameter for the fugacity model. For example, the atmospheric half-life of 2-methoxyethanol in air is judged to be between 30 and 100 hours. The geometric mean of this range, 55 hours, is used as an input parameter in the model. Conservative values for persistence were selected (i.e., longer rather than shorter half-lives) to ensure that persistence is not underestimated.

2.3.2.1 Multimedia exposure study

In a Canadian multimedia study, exposure to a number of volatile organic chemicals was measured for 50 participants across Canada (Conor Pacific Environmental Technologies, 1998). Thirty-five participants were randomly selected from the Greater Toronto area in Ontario, six participants from Queens Subdivision in Nova Scotia and nine from Edmonton, Alberta. For each participant, samples of drinking water and indoor, outdoor and personal air were collected over a 24-hour period. Samples of foods and beverages were not analysed for the determination of 2-methoxyethanol. The concentration of 2-methoxyethanol was below the method detection limit (0.06 μg/L) in all samples of drinking water. Similarly, it was not detected (<5 μg/m^3) in all samples of indoor, outdoor and personal air.

2.3.2.2 Ambient air

Other than the multimedia exposure study discussed in Section 2.3.2.1, no data were identified on the concentration of 2-methoxyethanol in ambient air in Canada.

2.3.2.3 Indoor air

In northern Italy, six indoor air samples were collected from homes in 1983–1984 and analysed for several organic pollutants by gas chromatography with mass spectrometric detection. The concentration of 2-methoxyethanol in one of the samples was 70 μg/m^3; in the remaining five samples, however, the concentration was below the limit of detection (not specified) (De Bortoli *et al.*, 1986).

In a study conducted in Germany, indoor air samples were collected following the sealing of wooden parqueted flooring in a school room with a product containing 2-methoxyethanol. The concentrations of 2-methoxyethanol in samples collected 10, 18, 25, 35, 52 and 90 days after sealing were 220, 150, 180, 160, 59 and 26 μg/m^3, respectively (Schriever and Marutzky, 1990).

2.3.2.3 Surface water

No data were identified on the concentration of 2-methoxyethanol in surface water in Canada or elsewhere.

2.3.2.4 Drinking water

2-Methoxyethanol was listed as a contaminant in drinking water samples analysed between June 1977 and November 1980 in a survey of 12 U.S. cities (Lucas, 1984). The concentration of the substance was not quantified but was less than 1 μg/L.

2.3.2.5 Soil

No data were identified on the concentration of 2-methoxyethanol in soil in Canada or elsewhere.

2.3.2.6 Food

No data on concentrations of 2-methoxyethanol in food were identified.

2.3.2.7 Consumer products

Glycol ethers are used as solvents in a number of consumer products, including paints, paint thinners and cleaning products. In Canada, there are no regulations concerning permissible levels of glycol ethers, including 2-methoxyethanol, in consumer products (Health Canada, 1998a). 2-Methoxyethanol was not detected in the emissions of 13 consumer products, including window cleaners, all-purpose cleaners, paints, nail polish removers and hair dye (classes of products reported to contain glycol ethers, based on available information), purchased in the Ottawa, Ontario, area (Cao, 1999). Glycol ethers, including 2-methoxyethanol, are not registered for use as an active ingredient in therapeutic products in Canada (Health Canada, 1998b). Of the cosmetic products registered for use in Canada, one nail polish remover was reported to contain 2-methoxyethanol in the range of 30–100% (Health Canada, 1998c); 2-methoxyethanol is also a component in an insecticidal formulation used on ornamental plants (Health Canada, 1998d).

In the United States, all-purpose cleaning products may contain concentrations of up to 2% 2-methoxyethanol, and metal cleaners may contain up to 6% (Flick, 1986, 1989). Versar Inc. (1986) reported varnish to contain 1.1% 2-methoxyethanol. In the Clinical Toxicology of Commercial Products database, one consumer product in the category of "coatings/inks" (which includes paints, varnishes, sealants, other coatings, marking pens and other similar items) and two products in the category of "coating thinners/strippers" were reported to emit 2-methoxyethanol (CARB, 1991). In a summary of the emissions of 2-methoxyethanol from materials listed in the NASA/McDonnell Douglas Materials Testing Data Base, emissions of 2-methoxyethanol from five adhesives were in the range of 1.2–30 µg/g product (median 2.1 µg/g product), those from one fabric were 0.33 µg/g product, and those from seven products in the category of "pens/inks" were in the range of 1.6–960 µg/g product (median 38 µg/g product) (CARB, 1991).

In a study conducted in Italy, 2-methoxyethanol was measured in the headspace analysis of a liquid wax for marble, ceramic and linoleum (Knöppel and Schauenburg, 1989). According to the 1993 Products Register in Sweden, 2-methoxyethanol was used in 23 products, totalling 260–262 tonnes of 2-methoxyethanol per year in these products (Johanson and Rick, 1996).

2.3.2.8 Fugacity modelling

Environmental concentrations of 2-methoxyethanol were estimated by ChemCan v. 4.0 modelling. This model is a Level III fugacity-based regional model developed to estimate the environmental fate of chemicals in Canada. ChemCan calculates the distribution of chemicals in the environmental media, the transport and transformation process rates, and average concentrations in any of 24 regions or ecozones of Canada. The highest reported recent release of 2-methoxyethanol in Canada is 17 tonnes, released into the air by one facility in southern Ontario in 1994 (NPRI, 1996). "Ontario – Mixed Wood Plain" was therefore selected as the geographic region for ChemCan modelling of 2-methoxyethanol. The input rate was 1.941 kg 2-methoxyethanol per hour, all to the atmosphere. Chemical input values were as follows: molecular weight, 76.1 g/mol; vapour pressure, 1300 Pa; water solubility, 500 000 mg/L; log K_{ow}, –0.77; Henry's law constant, 0.198 Pa·m^3/mol; half-life in air, 55 hours; half-life in water, 550 hours; half-life in soil, 550 hours; and half-life in sediment, 1700 hours. For Ontario – Mixed Wood Plain, environmental characteristics were as follows: total surface area, 169 000 km^2; proportion of area covered by water, 43.8%; average air height, 2 km; average water depth, 20 m; average soil depth, 10 cm; residence time in air, 1.71 days; residence time in water, 618 days; environmental temperature, 7.4°C.

Environmental concentrations of 2-methoxyethanol in southern Ontario predicted by ChemCan v. 4.0 modelling are as follows: 0.146 ng/m^3 in air; 4.8×10^{-5} µg/L in water; 9.4×10^{-4} ng/g dry weight in soil; and 2.34×10^{-5} ng/g dry weight in sediments. The ChemCan model estimates average concentrations throughout the region; therefore, actual concentrations in the vicinity of releases will be higher than those estimated by the model.

2.4 Effects characterization

2.4.1 Ecotoxicology

2.4.1.1 Terrestrial organisms

No information on the effects of 2-methoxyethanol on wildlife was identified. Data for experimental animals pertinent to the human health assessment are presented in Section 2.4.2. From the results of inhalation studies presented in that section, the animals that were most sensitive to airborne 2-methoxyethanol were New Zealand white rabbits. The lowest-observed-effect level (LOEL) for fetal toxicity (reduced weight, minor skeletal variations or testicular hypoplasia) was reported to be 10 ppm (31 mg/m^3, or 3.1×10^7 ng/m^3) (Hanley *et al.*, 1984a,b; see Section 2.4.2.6.1).

2.4.1.2 Aquatic organisms

Data on chronic toxicity have been identified only for protozoans and algae. The most sensitive organism reported was the flagellate protozoan, *Chilomonas paramecium*, with a 2-day toxicity threshold of 2200 µg/L, based on inhibition of cell multiplication (Bringmann and Kuehn, 1981). The most sensitive algal species reported was the blue-green alga, *Microcystis aeruginosa*, with an 8-day toxicity threshold of 100 000 µg/L, based on inhibition of cell multiplication (Bringmann and Kuehn, 1978). Data on acute toxicity have been reported for microorganisms, invertebrates and fish, although in many studies the LC_{50} for 2-methoxyethanol was above the highest concentration tested. For example, the 24-hour LC_{50} for goldfish (*Carassius auratus*) was >5 000 000 µg/L (Bridie *et al.*, 1979). The 96-hour LC_{50} for rainbow trout (*Oncorhynchus mykiss*) was 15 520 000 µg/L (Benville, 1974).

2.4.2 *Experimental animals and* in vitro

Identified information on the effects of 2-methoxyethanol in experimental animals is summarized in this section. As outlined in Section 1.0, this summary is based primarily on the review of relevant data prepared by BIBRA International, updated to include recent information identified in searches of on-line databases (BIBRA International, 1996/Health Canada, 1998). Original accounts were consulted as necessary for clarification.

In view of the limited objective of this screening assessment, presentation of data on health effects associated with 2-methoxyethanol is limited to an overview of the nature of the effects with emphasis on the lowest identified effect levels from repeated-exposure studies relevant to characterization of margins between estimates of population exposure and levels causing toxic effects; detailed descriptions of study protocols and results are included in the supporting documentation (BIBRA International, 1996/Health Canada, 1998; Health Canada, 1999).

2.4.2.1 Kinetics and metabolism

2-Methoxyethanol is extensively absorbed following oral, inhalation or dermal exposure and distributed extensively throughout the body, including the developing fetus, in which levels of metabolites may be greater than in the dams (Welsch and Sleet, 1987; Sleet *et al.*, 1988; Scott *et al.*, 1989). The major metabolic pathways of 2-methoxyethanol involve oxidation. In the first pathway, 2-methoxyethanol is rapidly metabolized via alcohol and aldehyde dehydrogenases to methoxyacetaldehyde (MALD), then methoxyacetic acid (MAA) (the likely active metabolites). The MAA is subsequently conjugated with glycine or *O*-demethylated, then oxidized to produce carbon dioxide; some MAA may also undergo Krebs cycle transformation. Alternatively, 2-methoxyethanol may be oxidized via microsomal P-450 mixed-function oxidases and *O*-demethylated to form formaldehyde and ethylene glycol. 2-Methoxyethanol may also be directly conjugated with sulphate or glucuronic acid.

In general, MAA (in free or conjugated form) was the principal metabolite detected in the urine of rats, mice and humans exposed by ingestion or inhalation; other urinary metabolites included ethylene glycol (particularly in rats following repeated exposure in drinking water) (Medinsky *et al.*, 1990) and products of Krebs cycle metabolism. The putatively toxic metabolite, MAA, is eliminated much more slowly in humans than in rats, with half-lives in the blood of 77 and 19 hours, respectively (Groeseneken *et al.*, 1989).

The acetate moiety of 2-methoxyethanol (2-methoxyethyl acetate), which is commonly encountered in the occupational environment, is rapidly hydrolysed to 2-methoxyethanol via esterases in several tissues in the body (WHO, 1990). For this reason, data on the toxicity of 2-methoxyethyl acetate have been included in this assessment.

2.4.2.2 Acute toxicity

2-Methoxyethanol is of low to moderate acute toxicity in experimental animals following oral, inhalation or dermal exposure, with oral LD_{50}s generally in the range of 1000 mg/kg-bw or more (Smyth *et al.*, 1941; Carpenter *et al.*, 1956; ECETOC, 1995). Sublethal effects following acute exposure to lower doses include reproductive toxicity in males (≥50 mg/kg-bw), alterations in hematological parameters (≥200 mg/kg-bw) and effects in the liver, thymus and spleen (300 mg/kg-bw) (Chapin and Lamb, 1984; Anderson *et al.*, 1987; Holloway *et al.*, 1990; Kawamoto *et al.*, 1990; Ku *et al.*, 1994). 2-Methoxyethanol did not induce skin sensitization and has low potential for causing skin or eye irritation (Carpenter and Smyth, 1946; Jacobs *et al.*, 1987, 1989; Jacobs, 1992; Devillers and Chessel, 1995; Zissu, 1995).

2.4.2.3 Short-term toxicity

The thymus, testes and blood have consistently been the most sensitive targets for adverse effects in rats repeatedly exposed over the short term to 2-methoxyethanol or 2-methoxyethyl acetate via ingestion, inhalation or dermal application (Miller *et al.*, 1981; Grant *et al.*, 1985; Fairhurst *et al.*, 1989; Feuston *et al.*, 1989; Kawamoto *et al.*, 1990; Exon *et al.*, 1991; Smialowicz *et al.*, 1991a; NTP, 1993; Butterworth *et al.*, 1995; Williams *et al.*, 1995). Reduced relative weight of the thymus was observed in rats orally administered 50 mg/kg-bw per day or more (4 days) or exposed to airborne concentrations of 300 ppm (933 mg/m^3) or greater (9 days), while histopathological changes were noted at higher exposure levels. Histopathological effects or reduced weights were also observed in the testes of rats exposed to around 88 mg/kg-bw per day or 300 ppm (933 mg/m^3) or greater for 9 or 10 days, while alterations in hematological parameters were reported in rats administered 70 mg/kg-bw per day or 300 ppm (933 mg/m^3) or more for 5 days or longer.

Although the database in mice is more limited, mice appear to be less sensitive than rats to induction of effects on these organs, as effects on the thymus, blood and testes were noted only at oral doses of 1000, 500 and 250 mg/kg-bw per day (≥4 days) (Nagano *et al.*, 1979, 1984; Miller *et al.*, 1981; Hong *et al.*, 1988) and airborne concentrations of 300, 300 and 1000 ppm (933, 933 and 3110 mg/m^3) (9 days), respectively (NTP, 1993). Available data on short-term toxicity in other experimental species are too limited for meaningful comparison.

2.4.2.4 Subchronic toxicity

2.4.2.4.1 Oral

The thymus, testes and blood were also the primary targets of 2-methoxyethanol-induced toxicity in rats exposed subchronically by gavage or in drinking water. Atrophy or decreased weight of the thymus and testes and alterations in hematological parameters (including mean hemoglobin concentration, packed cell volume, and red and white blood cell counts) were observed in rats administered oral doses of 285 mg/kg-bw per day (the lowest dose tested) or more for 6 weeks (U.S. EPA, 1992). Testicular degeneration and decreased thymus weights, along with effects on the blood (including anemia and reduced white blood cell and platelet counts), were also reported in F344/N rats exposed to 2-methoxyethanol in drinking water for 13 weeks at concentrations equivalent to doses of 71 mg/kg-bw per day or more (NTP, 1993). Similar to the results in short-term studies, B6C3F$_1$ mice were less sensitive than rats to effects induced by 2-methoxyethanol, as effects on the testes and thymus were noted only at doses of 530 and 990 mg/kg-bw per day and above, respectively, in drinking water for 13 weeks (hematological parameters were not examined); histopathological changes in the adrenal gland and splenic hematopoiesis were observed at doses as low as 492 mg/kg-bw per day (NTP, 1993).

2.4.2.4.2 Inhalation

Decreased thymus and testes weights, accompanied by histopathological changes in testes and alterations in several hematological (white blood cells, platelets and hemoglobin concentration) and clinical chemistry (total protein, albumin and globulin) parameters, were also observed in Sprague-Dawley rats exposed to 300 ppm (933 mg/m^3) 2-methoxyethanol by inhalation for 13 weeks. The only effect noted at lower concentrations was a decrease in body weight in females at 100 ppm (311 mg/m^3) (Miller *et al.*, 1983; Rao *et al.*, 1983; Hanley *et al.*, 1984a). These investigators observed New Zealand white rabbits to be more sensitive to the testicular toxicity of exposure to 2-methoxyethanol for 13 weeks, as degeneration was noted at concentrations as low as 30 ppm (93 mg/m^3), while lymphoid atrophy of the thymus occurred at 100 ppm (311 mg/m^3) and above. Effects on the blood (decreased counts of red and white blood cells and platelets and reduced hemoglobin concentration) were observed at 300 ppm (933 mg/m^3) (Miller *et al.*, 1983).

2.4.2.4.3 Dermal

Dermal exposure to 1000 mg/kg-bw per day for 13 weeks resulted in histopathological effects on the testes in guinea pigs, along with reduced organ and body weights and changes in hematological (mild anemia and reduced white blood cells) and clinical chemistry (blood enzymes and urinary calcium) parameters (Hobson *et al.*, 1986).

2.4.3.5 Chronic toxicity and carcinogenicity

No studies on the effects of chronic exposure to 2-methoxyethanol have been identified.

2.4.2.6 Genotoxicity

Although 2-methoxyethanol is not mutagenic in *in vitro* investigations, there is some indication that it induces clastogenic damage, and there is consistent evidence that the initial metabolite, MALD, is genotoxic in several cell lines. While the results of available *in vivo* studies suggest that 2-methoxyethanol is not genotoxic in somatic cells, there is some indication that it induces genetic effects in male germ cells.

2.4.2.6.1 *In vitro* studies

2-Methoxyethanol was not mutagenic in several strains of *Salmonella* (McGregor *et al.*, 1983; McGregor, 1984; Zeiger *et al.*, 1992; Hoflack *et al.*, 1995); although its primary metabolite, MAA, was also not mutagenic (McGregor *et al.*, 1983; Hoflack *et al.*, 1995), the acetaldehyde intermediate (MALD) was active in one strain, both with and without exogenous metabolic activation (Hoflack *et al.*, 1995). 2-Methoxyethyl acetate was not mutagenic in yeast (Abbondandolo *et al.*, 1980), although it caused chromosome malsegregation and aneuploidy (Zimmermann *et al.*, 1985; Whittaker *et al.*, 1989). 2-Methoxyethanol did not induce point mutations in mammalian cells *in vitro* (McGregor, 1984; Ma *et al.*, 1993; Chiewchanwit *et al.*, 1995), although the acetaldehyde metabolite induced an increase in HPRT and GPT mutations in Chinese hamster cells (Elias *et al.*, 1996).

There is some evidence that 2-methoxyethanol and its acetate cause increases in chromosomal aberrations in cultured mammalian (including human) cells; while the intermediate MALD was a potent inducer of chromosomal aberrations in various cell lines, MAA was inactive (Villalobos-Pietrini *et al.*, 1989; Chiewchanwit and Au, 1994; Elias *et al.*, 1996). Positive results were obtained for induction of micronuclei in mammalian cells for the parent compound as well as both metabolites, with the acetaldehyde being much more potent than either 2-methoxyethanol or MAA (Elias *et al.*, 1996). There was no convincing evidence that 2-methoxyethanol induced sister chromatid exchanges *in vitro*, although both MALD and MAA were active in this assay (Villalobos-Pietrini *et al.*, 1989; Loveday *et al.*, 1990; Chiewchanwit and Au, 1994; Elias *et al.*, 1996). Both 2-methoxyethanol and MALD induced aneuploidy or other mitotic aberrations *in vitro* (Zimmermann *et al.*, 1985; Whittaker *et al.*, 1989; Elias *et al.*, 1996).

2.4.2.6.2 *In vivo* studies

2-Methoxyethanol did not induce chromosomal aberrations in rats or mice following single or repeated exposure via inhalation, ingestion or intravenous injection (McGregor *et al.*, 1983; Au *et al.*, 1993), nor did 2-methoxyethyl acetate induce micronuclei in the bone marrow of hamsters administered a single dose via intraperitoneal injection (Basler, 1986). In the COMET assay, a single gavage dose of 500 mg

2-methoxyethanol/kg-bw per day or more caused DNA damage in bone marrow and haploid testicular cells of rats, along with a decrease in percentage head DNA content; however, the damage was transient, as it was not present 5 weeks after exposure (Anderson *et al.*, 1996). In addition, abnormalities in sperm morphology were reported in mice repeatedly exposed by inhalation to 500 ppm (1555 mg/m^3) 2-methoxyethanol for 5 days and in mice and rats following acute oral administration of 500 mg/kg-bw or more (McGregor *et al.*, 1983; Anderson *et al.*, 1987). However, the results of dominant lethal assays in rodents have been mixed (McGregor *et al.*, 1983; Rao *et al.*, 1983; Anderson *et al.*, 1987).

2.4.2.7 Developmental toxicity

2.4.2.7.1 Oral

2-Methoxyethanol and its principal metabolite, MAA, have consistently induced developmental toxicity in numerous oral studies in several species of experimental animals (although data are insufficient to evaluate variations in sensitivity across species), generally at doses or concentrations lower than those that are maternally toxic, and often at the lowest exposure level tested. For example, decreased fetal body weights were noted in rats repeatedly exposed to 2-methoxyethanol doses of 16 mg/kg-bw per day (the lowest dose) or more in the diet during gestation, with malformations being observed at doses of 31 mg/kg-bw per day or greater, while maternal toxicity was present only at higher doses (i.e., ≥140 mg/kg-bw per day) (Nelson *et al.*, 1989). Similar results were obtained in several other studies in rats exposed to 2-methoxyethanol in the diet or by gavage (single or repeated doses) (Ritter *et al.*, 1985; Toraason *et al.*, 1985, 1986a,b,c; Toraason and Breitenstein, 1988; Nelson *et al.*, 1991; Sleet *et al.*, 1996). In many of these studies, the cardiovascular system, kidney and skeletal system were the principal targets for 2-methoxyethanol-induced malformations; functional defects of the heart were also noted. Skeletal variations and delayed ossification were also reported in one study in mice repeatedly administered relatively low oral doses of 2-methoxyethanol (i.e., ≥31.25 mg/kg-bw per day), with more severe effects occurring at higher doses, which were also maternally toxic (Nagano *et al.*, 1981, 1984). Although the heart appeared to be a sensitive target organ in rats, this was not observed in mice, although fewer studies in mice were identified. However, the developing immune system was a target in one study in mice, based on effects on thymic cellularity, thymocyte antigen expression and liver prolymphoid cells (Holladay *et al.*, 1994). Oral administration of 12 mg 2-methoxyethanol/kg-bw per day or more for 25 days during pregnancy was maternally toxic and embryotoxic in cynomolgus monkeys; however, there was no definitive evidence of malformations at doses of up to 36 mg/kg-bw per day (Scott *et al.*, 1989).

2.4.2.7.2 Inhalation

In inhalation studies in rats, developmental effects, including increased resorptions, decreased pup or fetal weights and minor skeletal variations, were observed following repeated maternal exposure to 2-methoxyethanol concentrations of 50 ppm (156 mg/m^3) and above (Doe *et al.*, 1983; Hanley *et al.*, 1984a,b; Nelson *et al.*, 1984a), while more severe malformations, such as heart defects, were noted at

100 ppm (311 mg/m^3) or more (Nelson *et al.*, 1984a). Neurochemical changes and behavioural effects were observed in offspring of rats exposed to 25 ppm (78 mg/m^3) (Nelson *et al.*, 1984b). In single studies in mice and rabbits, LOELs for fetal toxicity (reduced weight, minor skeletal variations or testicular hypoplasia) were reported to be 50 and 10 ppm (156 and 31 mg/m^3), respectively, with no-observed-effect levels (NOELs) of 10 and 3 ppm (31 and 9 mg/m^3) (Hanley *et al.*, 1984a,b).

2.4.2.7.3 Dermal

Repeated dermal exposure of dams to doses of about 48 mg/kg-bw per day or more induced developmental toxicity (including malformations) in rats (Wickramaratne, 1986; Feuston *et al.*, 1990; Hellwig, 1993). 2-Methoxyethanol was also teratogenic in rats and mice when administered by other routes of exposure (i.e., intravenous, subcutaneous or intraperitoneal injection).

2.4.2.8 Reproductive toxicity

2.4.2.8.1 Reproductive effects in males

Oral

In the large number of relevant studies identified, 2-methoxyethanol was consistently toxic to the male reproductive system in multiple species exposed by all routes of administration. Effects on reproductive ability as well as reproductive organs have been observed, often at the lowest dose or concentration tested. Single or repeated oral administration of 2-methoxyethanol induced adverse effects on the testes (including weight and histopathological changes or biochemical indicators of testicular damage, such as urinary creatine) and/or various sperm parameters in every identified study in which these endpoints were examined, generally at doses of about 50 mg/kg-bw per day or more (Foster *et al.*, 1983, 1984; Chapin and Lamb, 1984; Chapin *et al.*, 1985a,b; Creasy *et al.*, 1985; Anderson *et al.*, 1987; Ghanayem and Chapin, 1990; Holloway *et al.*, 1990; Reader *et al.*, 1991; Smialowicz *et al.*, 1991a; Vachhrajani and Dutta, 1992; NTP, 1993; Ku *et al.*, 1994; Butterworth *et al.*, 1995; Aich and Manna, 1996; Timbrell *et al.*, 1996), although testicular effects were reportedly induced at 30 mg/kg-bw per day, based on a secondary account of a multigeneration study in which rats were exposed to 2-methoxyethanol in drinking water (Gulati *et al.*, 1990a,b). Reduced male fertility was also observed in several acute and short-term studies (in one study at a dose lower than those that induced histopathological changes in the testes [i.e., 50 mg/kg-bw per day]) (Chapin *et al.*, 1985a; Anderson *et al.*, 1987; Holloway *et al.*, 1990). In mice, effects on male fertility and reproductive organs were reported following short- and long-term administration of oral doses of 60 and 170 mg/kg-bw per day or more, respectively, although fewer studies in mice were identified (Nagano *et al.*, 1979, 1984; Anderson *et al.*, 1987; Chapin *et al.*, 1993; NTP, 1993). Similar effects on the testes or male reproductive ability were observed in short-term and subchronic studies in guinea pigs, rabbits and hamsters, with the lowest LOEL being 25 mg/kg-bw per day in rabbits (Nagano *et al.*, 1984; Ku *et al.*, 1994, 1995; Foote *et al.*, 1995; Berndtson and Foote, 1997).

Inhalation

Male reproductive toxicity (effects on organs, sperm parameters and/or fertility) was also induced in rats acutely or repeatedly exposed to 2-methoxyethanol by inhalation at 300 ppm (933 mg/m^3) or more (Doe *et al*., 1983; McGregor *et al*., 1983; Miller *et al*., 1983; Rao *et al*., 1983; Hanley *et al*., 1984a; Samuels *et al*., 1984; Lee and Kinney, 1989; Lee *et al*., 1989). Reproductive effects were also observed in male mice exposed to 500 ppm (1555 mg/m^3) 2-methoxyethanol (the only concentration tested) for 5 days (McGregor *et al*., 1983) and in male rabbits at 30 ppm (93 mg/m^3) (the lowest concentration tested) or more for 13 weeks (Miller *et al*., 1983).

Dermal

Repeated dermal exposure to 2-methoxyethanol for 7 days also induced effects on the testes, sperm parameters and fertility in rats; effects were noted at all doses tested when the site of administration was occluded (i.e., ≥625 mg/kg-bw per day) (Feuston *et al*., 1989).

2.4.2.8.2 Reproductive effects in females

Oral

Although not as extensively investigated, effects on the female reproductive system have also been associated with exposure to 2-methoxyethanol. Changes in estrous cyclicity and hormone levels as well as histopathological changes in the ovaries were observed in rats administered 100 and 300 mg/kg-bw per day or more, respectively, for several days, with a NOEL of 10 mg/kg-bw per day (Davis*et al*., 1997). Atrophy of female reproductive organs was also noted in rats exposed to oral doses of 297 mg/kg-bw per day or more for 13 weeks, although reduced body weight also occurred at these doses (NTP, 1993). Similarly, in mice, atrophy of the ovaries and altered estrous cycle were noted following subchronic oral administration of 2-methoxyethanol, but only at doses greater than those that induced these effects in rats (i.e., ≥1839 and ≥1194 mg/kg-bw per day, respectively; no effects were observed at lower exposure levels) (NTP, 1993). Conversely, however, Chapin *et al*. (1993) reported an increase in ovary weights in female mice at 636 mg/kg-bw per day in a multigeneration study.

Inhalation

No effects on female reproductive success or organs were observed in rats or rabbits exposed to 2-methoxyethanol by inhalation at concentrations of up to 300 ppm (933 mg/m^3) for 13 weeks (Miller *et al*., 1983; Rao *et al*., 1983; Hanley *et al*., 1984a).

2.4.2.9 Immunotoxicity

Exposure to 2-methoxyethanol or 2-methoxyethyl acetate significantly altered immune function in rats exposed orally or dermally. Although fewer studies are available, mice appear to be much less sensitive to the immunotoxicity of 2-methoxyethanol. Immunosuppression was observed in several studies in male and/or female rats (several strains) repeatedly administered oral doses of 50 mg 2-methoxyethanol/kg-bw per day or more over periods of 2–21 days, based on alterations in lymphoproliferative response of splenic lymphocytes to various mitogens, antibody plaque-forming cell response to antigens and other immune function parameters (Exon *et al.*, 1991; Smialowicz *et al.*, 1991a,b, 1992a,b, 1993; Riddle *et al.*, 1992, 1996; Williams *et al.*, 1995). In addition, thymus weights were decreased in most studies (at doses as low as 25 mg/kg-bw per day); occasionally, reductions in spleen weights or cellularity were also observed. In mice, however, there was no consistent evidence of immunosuppression at repeated doses of up to 1000 mg 2-methoxyethanol/kg-bw per day or 1920 mg MAA/kg-bw per day, although decreased thymus weights were observed and there was evidence of enhancement or modulation of immune system response in some studies (House *et al.*, 1985; Kayama *et al.*, 1991; Riddle *et al.*, 1992, 1996; Smialowicz *et al.*, 1992b, 1994). The results of studies in rats in which enzyme inhibitors were administered indicated that the parent compound was not in itself immunotoxic, but that both the aldehyde and acid metabolites (MALD and MAA) suppressed immune system function (Smialowicz *et al.*, 1991a,b, 1993).

2.4.2.10 Neurotoxicity

Although the database is limited to two studies in rats and a single study in mice, 2-methoxyethanol appears to induce neurological effects following acute or short-term inhalation exposure, including inhibition of conditioned avoidance response, increased barbiturate-induced sleeping time or partial hind limb paralysis at concentrations of 125 ppm (389 mg/m^3) or greater and altered enzyme activities in the brain at 50 ppm (156 mg/m^3) or more (Goldberg *et al.*, 1962; Savolainen, 1980). In addition, as noted above in Section 2.4.2.7.2, repeated exposure of pregnant rats to 25 ppm (78 mg/m^3) induced effects on avoidance conditioning and neurochemical changes in the offspring (Nelson *et al.*, 1984b).

2.4.3 Humans

2.4.3.1 Case reports

Several cases of adverse health effects following incidental or occupational exposure to 2-methoxyethanol have been identified in the literature. In general, effects on the nervous, respiratory and hematological systems (which appeared to be reversible after several months) have been associated with exposure in the work environment via inhalation and dermal contact. Although data on exposure levels were sparse, workplace concentrations in these case reports ranged from 8 to 3960 ppm (25 to 12 316 mg/m^3) (Zavon, 1963; Ohi and Wegman, 1978); however, these workers were also exposed to other substances in addition to 2-methoxyethanol. Abnormal development of male reproductive organs was reported in two boys whose mother had been intensively exposed to 2-methoxyethyl acetate via inhalation and dermal contact during pregnancies (no quantitative estimates of exposure were presented) (Bolt and Golka, 1990).

2.4.3.2 Clinical studies

In the only clinical study identified (which was primarily intended to investigate the toxicokinetics of 2-methoxyethanol in humans), there were no changes in pulmonary ventilation or heart rates in seven male volunteers exposed to 5 ppm (16 mg/m^3) 2-methoxyethanol for 4 hours (Groeseneken *et al.*, 1989).

2.4.3.3 Epidemiological studies

Several epidemiological studies have been conducted in which a potential association between either glycol ethers as a class or an industrial process in which glycol ethers are used and various health endpoints (including hematological, immunological, neurological or reproductive and developmental effects as well as acute myeloid leukemia) has been investigated. In these studies, there was no conclusive evidence that occupational exposure to 2-methoxyethanol specifically induces adverse health effects in humans, as all of the populations studied were also exposed to other solvents. However, available limited data from several cross-sectional surveys are suggestive of an association between hematological abnormalities, as well as effects on the immune and nervous systems, and exposure to 2-methoxyethanol along with other substances via inhalation and dermal contact. Alterations in various blood parameters (including red blood cell, white blood cell [or specifically granulocyte or polymorphonuclear leukocyte] or platelet counts and hemoglobin levels) were observed in workers exposed to 2-methoxyethanol while treating collars in a shirt factory (25–76 ppm or 78–236 mg/m^3; Greenburg *et al.*, 1938), painting in a shipyard (up to 5.7 ppm or 17.7 mg/m^3; Welch and Cullen, 1988) or laying parquet floors (up to 48 ppm or 149 mg/m^3; Denkhaus *et al.*, 1986) or in the manufacture and packaging of the compound (up to 20 ppm or 62 mg/m^3; Cook *et al.*, 1982). Significant differences in the distribution of lymphocyte subpopulations were also noted in the parquet floor workers compared with controls (Denkhaus *et al.*, 1986).

Decreased sperm production was also noted in a cross-sectional study of 73 shipyard painters exposed to 2-methoxyethanol along with 2-ethoxyethanol (Welch *et al.*, 1988), while difficulty in having children was reported in 40 men employed in the manufacture or packaging of 2-methoxyethanol compared with 25 unexposed workers, although there were no significant differences in sperm count or hormone levels in small subgroups of these employees (Cook *et al.*, 1982). With respect to potential effects on female reproduction, although the results of a historical cohort study in 891 women indicated that there was an increase in spontaneous abortions in those engaged in the fabrication departments at 14 semiconductor plants compared with non-fabrication workers (relative risk [RR] = 1.45, 95% confidence interval [CI] = 1.02–2.06), particularly in those exposed to glycol ethers (RR = 1.56, 95% CI = 1.02–2.31; RR = 3.38, 95% CI = 1.61–5.73 for those with the highest qualitative exposure scores), it is not possible to discern the role of 2-methoxyethanol specifically, in view of the lack of data on exposure. In the prospective portion of this study, involving 481 women, there was again a significant association between occurrence of spontaneous abortions and exposure to glycol ethers (RR = 2.0, 95% CI = 1.46–2.75) and a non-significant reduction in fecundability (p = 0.08) (Beaumont *et al.*, 1995; Schenker *et al.*, 1995; Swan *et al.*, 1995; Schenker, 1996; Swan and Forest, 1996).

2.4.4 Abiotic atmospheric effects

Worst-case calculations were made to determine if 2-methoxyethanol has the potential to contribute to depletion of stratospheric ozone, ground-level ozone formation or climate change (Bunce, 1996).

The Ozone Depletion Potential (ODP) is 0, as 2-methoxyethanol is not a halogenated compound.

The Photochemical Ozone Creation Potential (POCP) was estimated to be 61 (relative to the reference compound ethene, which has a POCP of 100), based on the following formula:

$$\mathrm{POCP} = (k_{\text{2-methoxyethanol}}/k_{\text{ethene}}) \times (M_{\text{ethene}}/M_{\text{2-methoxyethanol}}) \times 100$$

where:

- $k_{\text{2-methoxyethanol}}$ is the rate constant for the reaction of 2-methoxyethanol with OH radicals (1.4×10^{-11} cm^3/mol per second),
- k_{ethene} is the rate constant for the reaction of ethene with OH radicals (8.5×10^{-12} cm^3/mol per second),
- M_{ethene} is the molecular weight of ethene (28.1 g/mol), and
- $M_{\text{2-methoxyethanol}}$ is the molecular weight of 2-methoxyethanol (76 g/mol).

The Global Warming Potential (GWP) was calculated to be 8.4×10^{-5} (relative to the reference compound CFC-11, which has a GWP of 1), based on the following formula:

$$\mathrm{GWP} = (t_{\text{2-methoxyethanol}}/t_{\text{CFC-11}}) \times (M_{\text{CFC-11}}/M_{\text{2-methoxyethanol}}) \times (S_{\text{2-methoxyethanol}}/S_{\text{CFC-11}})$$

where:

- $t_{\text{2-methoxyethanol}}$ is the lifetime of 2-methoxyethanol (0.0028 years),
- $t_{\text{CFC-11}}$ is the lifetime of CFC-11 (60 years),
- $M_{\text{CFC-11}}$ is the molecular weight of CFC-11 (137.5 g/mol),
- $M_{\text{2-methoxyethanol}}$ is the molecular weight of 2-methoxyethanol (76 g/mol),
- $S_{\text{2-methoxyethanol}}$ is the infrared absorption strength of 2-methoxyethanol (2389/cm^2 per atmosphere, default), and
- $S_{\text{CFC-11}}$ is the infrared absorption strength of CFC-11 (2389/cm^2 per atmosphere).

These figures suggest that 2-methoxyethanol does not contribute to stratospheric ozone depletion, that its potential contribution to climate change is negligible and that its potential contribution to ground-level ozone formation is moderate. The magnitude of these effects would depend on the concentration of 2-methoxyethanol in the atmosphere, and concentrations of the substance in air in Canada are estimated to be very low. The contribution of 2-methoxyethanol to ozone formation is therefore considered negligible compared with those of other more abundant smog-forming substances, such as the reference compound, ethene (Bunce, 1996).

3.0 PROPOSED ASSESSMENT OF "TOXIC" UNDER CEPA 1999

3.1 CEPA 1999 64(a): Environment

The environmental risk assessment of a PSL substance is based on the procedures outlined in Environment Canada (1997a). Analysis of exposure pathways and subsequent identification of sensitive receptors are used to select environmental assessment endpoints (e.g., adverse reproductive effects on sensitive fish species in a community). For each endpoint, a conservative Estimated Exposure Value (EEV) is selected and an Estimated No-Effects Value (ENEV) is determined by dividing a Critical Toxicity Value (CTV) by an application factor. A conservative (or hyperconservative) quotient (EEV/ENEV) is calculated for each of the assessment endpoints in order to determine whether there is potential ecological risk in Canada. If these quotients are less than one, it can be concluded that the substance poses no significant risk to the environment, and the risk assessment is completed. If, however, the quotient is greater than one for a particular assessment endpoint, then the risk assessment for that endpoint proceeds to an analysis where more realistic assumptions are used and the probability and magnitude of effects are considered. This latter approach involves a more thorough consideration of sources of variability and uncertainty in the risk analysis.

3.1.1 Assessment endpoints

In Canada, most environmental releases of 2-methoxyethanol are to the atmosphere. Based on its predicted environmental partitioning, assessment endpoints for 2-methoxyethanol relate to terrestrial organisms, including terrestrial wildlife and soil organisms, and aquatic organisms.

3.1.2 Environmental risk assessment

3.1.2.1 Terrestrial organisms

3.1.2.1.1 Wildlife

For a conservative risk characterization for wildlife, the EEV is 0.146 ng/m^3, the estimated concentration of 2-methoxyethanol in air using ChemCan modelling based on reported releases in 1994. This value is believed to be conservative because releases of 2-methoxyethanol in Canada appear to have significantly decreased since 1994.

The CTV is 10 ppm (3.1×10^7 ng/m^3), the LOEL in an inhalation study with rabbits (Hanley *et al.*, 1984a,b), based on fetal toxicity. Dividing this CTV by a factor of 10 (to account for the extrapolation from laboratory to field conditions and interspecies and intraspecies variations in sensitivity) gives an ENEV of 1 ppm (3.1×10^6 ng/m^3).

The conservative quotient is calculated as follows:

$$\text{Quotient} = \frac{\text{EEV}}{\text{ENEV}}$$

$$= \frac{0.146 \text{ ng/m}^3}{3.1 \times 10^6 \text{ ng/m}^3}$$

$$= 4.7 \times 10^{-8}$$

Therefore, concentrations of 2-methoxyethanol in air in Canada are unlikely to cause adverse effects on populations of wildlife. Concentrations of 2-methoxyethanol in Canadian indoor and outdoor air samples were all below the detection limit of 5 µg/m^3 (5 × 10^3 ng/m^3) (Conor Pacific Environmental Technologies, 1998), a value that is well below the ENEV. Maximum reported concentrations of 2-methoxyethanol in indoor air samples from Italy (70 µg/m^3 or 7 × 10^4 ng/m^3; De Bortoli *et al.*, 1986) and Germany (220 µg/m^3 or 2.2 × 10^5 ng/m^3; Schriever and Marutzky, 1990) were also below the ENEV.

3.1.2.1.2 Soil organisms

For a conservative risk characterization for soil organisms, the EEV is 9.4 × 10^{-4} ng/g dry weight, the estimated concentration of 2-methoxyethanol in soil using ChemCan modelling based on reported releases in 1994. This value is believed to be conservative because releases of 2-methoxyethanol in Canada appear to have significantly decreased since 1994.

No information was identified regarding the toxicity of 2-methoxyethanol to soil organisms. Van Leeuwen *et al.* (1992) used quantitative structure–activity relationships to estimate that a sediment concentration of 1800 ng 2-methoxyethanol/g would be hazardous to 5% of benthic species. Using this sediment HC_5 value as a CTV and an application factor of 100 (to account for the extrapolation from benthic to soil organisms) gives an ENEV of 18 ng/g for soil organisms.

The conservative quotient is calculated as follows:

$$\text{Quotient} = \frac{\text{EEV}}{\text{ENEV}}$$

$$= \frac{9.4 \times 10^{-4} \text{ ng/g}}{18 \text{ ng/g}}$$

$$= 5.2 \times 10^{-5}$$

Therefore, concentrations of 2-methoxyethanol in soil in Canada appear to be unlikely to cause adverse effects on populations of soil organisms.

3.1.2.2 Aquatic organisms

For a conservative risk characterization for aquatic organisms, the EEV is 4.8×10^{-5} µg/L, the estimated concentration of 2-methoxyethanol in water using ChemCan modelling based on reported releases in 1994. This value is believed to be conservative because releases of 2-methoxyethanol in Canada appear to have significantly decreased since 1994.

The CTV for aquatic organisms is 2200 µg/L, the 2-day toxicity threshold for the flagellate protozoan, *Chilomonas paramecium*, based on inhibition of cell multiplication. Dividing this CTV by a factor of 10 (to account for the extrapolation from laboratory to field conditions and interspecies and intraspecies variations in sensitivity) gives an ENEV of 220 µg/L.

The conservative quotient is calculated as follows:

$$\text{Quotient} = \frac{\text{EEV}}{\text{ENEV}}$$

$$= \frac{4.8 \times 10^{-5}\ \mu\text{g/L}}{220\ \mu\text{g/L}}$$

$$= 2.2 \times 10^{-7}$$

Therefore, concentrations of 2-methoxyethanol in water in Canada appear to be unlikely to cause adverse effects on populations of aquatic organisms.

3.1.2.3 Discussion of uncertainty

There are several sources of uncertainty in this environmental risk assessment. Very few data were identified on environmental concentrations of 2-methoxyethanol in Canada or elsewhere. The ChemCan v. 4.0 model was therefore used to estimate environmental concentrations of 2-methoxyethanol in the various environmental compartments, based on the highest reported recent release of the substance in Canada, which occurred in 1994. These values are believed to be conservative because releases of 2-methoxyethanol in Canada appear to have significantly decreased since then and because conservative estimates of persistence were used as inputs to the model. Kane (1993) compared measured environmental concentrations of five industrial chemicals and six pesticides with environmental concentrations estimated for the substances by the ChemCan model. Sixty percent of the measured environmental concentrations were within 1 order of magnitude of predicted values, and 75% were within 2 orders of magnitude. The few data that are available on the concentration of 2-methoxyethanol in the Canadian environment, including indoor air and tap water, support the conclusion that levels are very low.

No information was identified regarding the toxicity of 2-methoxyethanol to soil organisms or to terrestrial wildlife through atmospheric exposure. An estimation of a hazardous concentration to benthic species was the basis for the assessment of risk to soil organisms. The results of an inhalation toxicity study using a laboratory strain of rabbits were used for the assessment of risk to wildlife. To account for these uncertainties, application factors were used in the environmental risk assessment to derive ENEVs.

Usage and environmental releases of 2-methoxyethanol in Canada appear to be declining. Conservative risk quotients are very small for all environmental assessment endpoints. Therefore, despite the data gaps regarding the environmental concentrations and effects of 2-methoxyethanol on soil organisms and terrestrial wildlife, the data available at this time are considered adequate for drawing a conclusion about the environmental risk of the substance in Canada.

CEPA 1999 64(b): Environment upon which life depends

2-Methoxyethanol does not deplete stratospheric ozone, and its potential for contributing to climate change is negligible. The potential of 2-methoxyethanol for creation of photochemical ozone (smog) is moderate, but the low quantities of 2-methoxyethanol in the atmosphere are unlikely to make its contribution significant relative to that of other smog-forming substances.

3.3 CEPA 1999 64(c): Human health

3.3.1 Estimates of potential exposure in humans

The limitations of the available monitoring data for 2-methoxyethanol preclude the development of reliable estimates of typical exposure of the general population; instead, worst-case or bounding estimates of exposure to 2-methoxyethanol from environmental media and consumer products have been developed in order to characterize potential exposure from these pathways.

Because most of the consumer products for which suitable data are available are used primarily by adults, the estimated exposures have been derived for this age class only, although the limitations of the available data preclude very confident estimation of intake for even one age group. (The differences among age classes in intake from a given medium, as a result of age-specific differences in intakes of environmental media and in body weight, would be small in relation to the variation in exposure from the various sources, in any case.) Worst-case or bounding estimates of intake of 2-methoxyethanol by Canadian adults from various sources and the assumptions upon which they are based are summarized in Table 1.

The only environmental media for which available monitoring data allowed even crude estimation of exposure were air and water. These estimates are based on the limits of detection in air and tap water from the Canadian multimedia study in which concentrations of 2-methoxyethanol were below the limit of detection in all of the samples of air and tap water that were analysed for 50 participants (Conor Pacific Environmental Technologies, 1998). However, although the limits of detection for this substance were relatively high, the lack of detection in these media is not surprising in view of the decline in use and production of 2-methoxyethanol in Canada over the last several years. Based on these values, the average adult in Canada would be exposed to airborne levels of 2-methoxyethanol no greater than 5 $\mu g/m^3$ and would not ingest more than 0.013 µg/kg-bw per day, although it is recognized that these values likely overestimate exposure. In addition, concentrations of 2-methoxyethanol in ambient air and surface water predicted by fugacity modelling (presented in Section 2.3.2.8), based on the highest reported release in recent years, were several orders of magnitude below these detection limits. Therefore, the estimated worst-case or bounding estimates of intake from air (0.0011 mg/kg-bw per day) and water (0.000 013 mg/kg-bw per day) are substantially less than those for consumer products.

Although no monitoring data are available, food is unlikely to be a principal source of exposure to 2-methoxyethanol in humans, since it is released primarily to air from industrial activities and consumer products (no releases to other media have been reported). It is unlikely to partition to food from air due to its high volatility and very low octanol/water partition coefficient (log K_{ow} of −0.77). [In fact, even if intake in food is estimated on the basis of extrapolation from the results of the fugacity modelling, this value would still be several orders of magnitude less than the worst-case scenarios calculated for air and drinking water on the basis of the limit of detection in the multimedia study.] Likewise, exposure to 2-methoxyethanol in soil is likely to be negligible in comparison to that in air, based on its release patterns and physical/chemical properties and the results of fugacity modelling.

Direct exposure to 2-methoxyethanol can result from the use of a variety of consumer products containing these substances. Both inhalation and dermal absorption are expected to be important routes of exposure for most consumer products, since many of those products expected to contain 2-methoxyethanol can contact the skin. Estimated intakes from the few products for which quantitative data were identified are presented in Table 1. However, since information on current compositions and use patterns of these products in Canada is extremely limited, these values likely overestimate current exposures considerably in view of the decline in use of this compound in many countries. The highest estimated worst-case intake of 2-methoxyethanol for consumer products was for nail polish remover (12.5 mg/kg-bw per day). This estimate was developed from product use scenarios (U.S. EPA, 1997), assuming 100% of the applied compound was absorbed, and refers to dermal absorption only. Upper-bounding estimates of intake of 2-methoxyethanol from exposure to household cleaning products and varnish were developed from product use scenarios (Versar Inc., 1986), assuming 100% absorption for the product contacting the skin and for the inhaled product (in view of lack of adequate data to support a more refined estimate). Worst-case estimates of indoor air concentrations resulting from the use of products such as an all-purpose spray cleaner were calculated to be up to 76 mg/m^3.

It should be noted that these estimates have been made for only a limited range of media and products for which at least some data were available. In addition, they do not represent typical exposures, since the limitations of the available data preclude development of such estimates; most are instead maximal or near-maximal estimates of potential exposure.

3.3.2 Human health risk characterization

As discussed in Section 1.0, a screening approach was adopted for assessment of 2-methoxyethanol as a Priority Substance under CEPA 1999, in view of the paucity of data upon which to base estimates of population exposure as well as the considerable decline in the production and use of this substance in recent years. In this approach, estimates of worst-case exposure are compared with conservative effect levels for critical effects in order to determine the margin between these estimates. On this basis, areas where additional information may be required to ensure that current measures for reduction of population exposure are sufficiently protective may be identified.

Exposure to 2-methoxyethanol has been associated with a range of adverse health effects in experimental animals, including effects on weights and histopathology of various organs, hematological, immunological and neurological effects, and reproductive and developmental toxicity, including teratogenicity. In many studies, effects were observed at the lowest dose or concentration tested. For example, the lowest reported LOELs (oral exposure) for developmental toxicity were 12 and 16 mg/kg-bw per day in monkeys and rats (lower doses were not investigated), respectively, with increased malformations occurring in rats at 31 mg/kg-bw per day (in the absence of maternal toxicity) (Nelson *et al*., 1989; Scott *et al*., 1989). In inhalation studies, developmental effects were observed at concentrations of 10 ppm (31 mg/m^3) or more in rabbits, but not at 3 ppm (9 mg/m^3) (Hanley *et al*., 1984a,b). The lowest reported LOEL for developmental toxicity (including malformations) following dermal exposure was approximately 48 mg/kg-bw per day in rats, the lowest dose tested in the study (Hellwig, 1993). There is some indication that 2-methoxyethanol may be weakly genotoxic in somatic cells, likely through activation to the intermediate acetaldehyde metabolite, and that it causes genetic damage to male germ cells in rats at high doses or concentrations (i.e., >500 mg/kg-bw per day) (McGregor *et al*., 1983; Anderson *et al*., 1987, 1996), which is in concordance with the observed effects on male reproduction.

Data from case reports or other epidemiological studies are not conclusive with respect to evaluation of adverse effects associated with exposure to 2-methoxyethanol in humans, although they are suggestive of effects on the hematological system and, perhaps, on reproduction in men and women employed in occupations involving exposure to 2-methoxyethanol as well as other substances. Such potential associations would be consistent with the observations in experimental animals.

In available studies, therefore, 2-methoxyethanol has induced a wide range of adverse effects, including those considered to be severe and irreversible (e.g., teratogenicity), with some occurring at relatively low doses. Although information on the mode(s) of induction of these effects has not been critically examined for the purposes of this assessment, it cannot be precluded at this time that there may be some probability of adverse effects occurring at any level of exposure, as there is some evidence of interaction with genetic material, at least at high doses, particularly for the metabolite MALD.

Based on comparison of the lowest LOEL reported in oral studies in animals (i.e., 12 mg/kg-bw per day or 12 000 µg/kg-bw per day), since a NOEL was not identified in these studies, with the worst-case exposure scenario for ingestion of 2-methoxyethanol in drinking water of 0.013 µg/kg-bw per day, the margin between exposure and effect level is about 6 orders of magnitude. With respect to inhalation, comparison of a NOEL for toxic effects of 3 ppm or 9 mg/m^3 (9000 µg/m^3) with a worst-case exposure level in air (5 µg/m^3) indicates that the margin would be about 3 orders of magnitude. However, estimates of exposure to 2-methoxyethanol through use of some consumer products (based on the very limited information available) approach or are within a few orders of magnitude of effect levels for adverse health effects in animals. For example, estimated intake through use of a nail polish remover containing up to 100% 2-methoxyethanol could range up to 12.5 mg/kg-bw per day (i.e., exposure through use of this product would be similar to the lowest effect level for oral exposure and within an order of magnitude of a dermal LOEL of 48 mg/kg-bw per day). Use of other products, such as an all-purpose spray cleaner, could result in exposure to concentrations in indoor air of up to 76 mg/m^3, which would exceed the NOEL for developmental toxicity. Margins between exposure and lowest reported effect level for severe, irreversible effects (i.e., teratogenicity) would also be less than an order of magnitude.

Therefore, on the basis of these values, while the margin between levels of exposure that induce effects in experimental animals and estimates of exposure from air and drinking water may be large, the margin between effect levels and worst-case estimates of exposure from some consumer products may be insufficient to address the requisite elements of uncertainty (e.g., interspecies and intraspecies [interindividual] variation) against which adequacy would be judged.

3.3.3 Uncertainties and degree of confidence in the human health risk characterization

Due to the paucity of data on levels of 2-methoxyethanol in environmental media in Canada, there is a high degree of uncertainty in the estimates of exposure to this substance that are presented in this assessment. While a worst-case exposure scenario was determined on the basis of the detection limits in a small number of samples in a multimedia study, it is not known if these values grossly overestimate environmental levels or if the general population is exposed to levels approaching these values, although predicted concentrations in ambient air and drinking water (using fugacity modelling) were several orders of magnitude less than these detection limits. Although environmental levels are expected to decline in the wake of reduced use of 2-methoxyethanol by many countries, there is some uncertainty as to whether or not such a decline has occurred in environmental media in Canada due to lack of adequate monitoring data. In addition, the only media in which 2-methoxyethanol was measured in the multimedia study were drinking water and air, although there is a moderate degree of certainty that food and soil do not represent important sources of exposure, based on the physical and chemical properties of this substance, the sources of release to the environment, as well as the results of fugacity modelling.

There is a low degree of confidence in the estimates of exposure to 2-methoxyethanol through the use of various consumer products, due to the large uncertainties concerning the presence and levels of the substance in products currently available in Canada. For example, it should be noted that 2-methoxyethanol was not detected in emissions from similar products recently investigated by Health Canada (Cao, 1999), and thus these estimates are likely very conservative. These estimates were also calculated assuming 100% absorption through the skin, in view of the lack of adequate data to support a lower percent absorption. Therefore, it is considered important to determine whether or not 2-methoxyethanol is present in consumer products currently available in Canada and, if so, to investigate levels of 2-methoxyethanol in and the use patterns of such products, in order to better characterize the risk to human health.

There is a moderate to high degree of confidence in the available data to serve as a basis for hazard characterization for the non-neoplastic effects associated with exposure to 2-methoxyethanol, as hematological, immunological, reproductive and developmental effects (including teratogenicity at relatively low exposure levels) have been repeatedly demonstrated in acute, short-term and subchronic studies in experimental animals, although no chronic studies have been identified and epidemiological data are inadequate (although it is notable that, even though confounded by concurrent exposures to other substances, the results of the available epidemiological studies are consistent with those from studies in animals). However, in the absence of any long-term investigations in animals, and in view of the limited evidence of weak genotoxicity (and stronger evidence of the genotoxicity of the initial metabolite), there is some uncertainty with regard to the potential of 2-methoxyethanol to induce neoplastic effects.

3.4 Proposed conclusions

CEPA 1999 64(a): Based on conservative estimates of exposure and effects in Canada, risk quotients for terrestrial wildlife, soil organisms and aquatic organisms are less than one. The environmental risks associated with estimated concentrations of 2-methoxyethanol likely to be found in Canada therefore appear to be low. Therefore, available data indicate that it is unlikely that 2-methoxyethanol is entering or may enter the environment in a quantity or concentration or under conditions that have or may have an immediate or long-term harmful effect on the environment or its biological diversity, and it is proposed that it should not be considered "toxic" as defined in CEPA 1999 Paragraph 64(a).

CEPA 1999 64(b): 2-Methoxyethanol is not involved in the depletion of stratospheric ozone and likely does not contribute significantly to climate change. Because of its very low estimated concentration in air in Canada, it is unlikely to play a significant role in tropospheric ozone production. Therefore, based on available data, it has been concluded that 2-methoxyethanol is not entering the environment in a quantity or concentration or under conditions that constitute or may constitute a danger to the environment on which life depends, and it is proposed that it should not be considered "toxic" as defined in CEPA 1999 Paragraph 64(b).

CEPA 1999 64(c): There is considerable evidence that 2-methoxyethanol causes a range of adverse effects in experimental animals (including those considered to be severe and irreversible, such as teratogenicity), some for which it cannot be precluded that there is some probability of occurrence at any level of exposure. In addition, the margins between worst-case estimates of exposure to 2-methoxyethanol via some consumer products (although data are extremely limited) and effect levels for adverse health effects in experimental animals are considered inadequate to address requisite elements of uncertainty. Thus, on the basis of available data, 2-methoxyethanol is considered to constitute a danger in Canada to human life or health and is, therefore, deemed "toxic" under Paragraph 64(c) of CEPA 1999.

Proposed overall conclusion: Based on critical assessment of relevant information, 2-methoxyethanol is considered to be "toxic" as defined in Section 64 of CEPA 1999.

3.5 Considerations for follow-up (further action)

While 2-methoxyethanol appears not to be produced in Canada currently, information on its use, in particular on its potential presence in consumer products, is sparse. It is recommended, therefore, that additional information be acquired on patterns of use of the compound in Canada and its potential presence in consumer products, as a basis for risk management.

Depending upon patterns of use, it may be necessary to conduct a fuller assessment of the potential adverse effects of 2-methoxyethanol, since the conclusions included herein are based not only on limited data on potential for exposure but also on screening of available data on toxicity. However, in view of the profile of inherent toxicity of 2-methoxyethanol, it would be prudent to eliminate or reduce, to the extent possible, the potential for exposure of the general population to this compound.

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APPENDIX A: Search strategies employed for identification of relevant data

Environmental assessment

Data relevant to the assessment of whether 2-methoxyethanol is "toxic" to the environment under CEPA were identified from existing review documents, published reference texts and on-line searches, conducted between January and May 1996, of the following databases: ASFA (Aquatic Sciences and Fisheries Abstracts, Cambridge Scientific Abstracts; 1990–1996), BIOSIS (Biosciences Information Services; 1990–1996), CAB (Commonwealth Agriculture Bureaux; 1990–1996), CESARS (Chemical Evaluation Search and Retrieval System, Ontario Ministry of the Environment and Michigan Department of Natural Resources; 1996), CHRIS (Chemical Hazard Release Information System; 1964–1985), Current Contents (Institute for Scientific Information; 1993 – January 15, 1996), ELIAS (Environmental Library Integrated Automated System, Environment Canada library; January 1996),Enviroline (R.R. Bowker Publishing Co.; November 1995 – June 1996), Environmental Abstracts (1975 – February 1996), Environmental Bibliography (Environmental Studies Institute, International Academy at Santa Barbara; 1990–1996), GEOREF (Geo Reference Information System, American Geological Institute; 1990–1996), HSDB (Hazardous Substances Data Bank, U.S. National Library of Medicine; 1996), Life Sciences (Cambridge Scientific Abstracts; 1990–1996), NTIS (National Technical Information Service, U.S. Department of Commerce; 1990–1996), Pollution Abstracts (Cambridge Scientific Abstracts, U.S. National Library of Medicine; 1990–1996), POLTOX (Cambridge Scientific Abstracts, U.S. National Library of Medicine; 1990–1995), RTECS (Registry of Toxic Effects of Chemical Substances, U.S. National Institute for Occupational Safety and Health; 1996), Toxline (U.S. National Library of Medicine; 1990–1996), TRI93 (Toxic Chemical Release Inventory, U.S. Environmental Protection Agency, Office of Toxic Substances; 1993), USEPA-ASTER (Assessment Tools for the Evaluation of Risk, U.S. Environmental Protection Agency; up to December 21, 1994), WASTEINFO (Waste Management Information Bureau of the American Energy Agency; 1973 – September 1995) and Water Resources Abstracts (U.S. Geological Survey, U.S. Department of the Interior; 1990–1996). Reveal Alert was used to maintain an ongoing record of the current scientific literature pertaining to the potential environmental effects of 2-methoxyethanol. Data obtained after September 30, 1999, were not considered in this assessment.

In addition, a survey of Canadian industry was carried out under the authority of Section 16 of CEPA (Environment Canada, 1997b, 1997c). Targeted companies with commercial activities involving more than 1000 kg of 2-methoxyethanol were required to supply information on uses, releases, environmental concentrations, effects or other data that were available to them for 2-methoxyethanol.

Health assessment

In addition to studies included in the review prepared by BIBRA International, recent data have been identified through searching the following databases beginning in August 1996 using the chemical name or the CAS number for both 2-methoxyethanol and 2-methoxyethyl acetate: CAB Abstracts, Canadian Research Index, DIALOG (Cancerlit, Environmental Bibliography, Waternet, Water Resources Abstracts, Enviroline, Pollution Abstracts and NTIS), Food Science and Technology Abstracts, Medline, Toxline Plus and TOXNET (CCRIS [Chemical Carcinogenesis Research Information System, U.S. National Cancer Institute], GENE-TOX [Genetic Toxicology, U.S. Environmental Protection Agency] and EMIC [Environmental Mutagen Information Center database, Oak Ridge National Laboratory]). Data acquired as of October 1999 were considered for inclusion in this draft.

As well as these databases, officials at the Product Safety Bureau and Drugs Directorate of Health Canada, along with the Pest Management Regulatory Agency, were contacted to obtain information relevant to this assessment.

Table 1: Worst-case/bounding estimates of intake of 2-methoxyethanol by adult Canadians

Exposure medium	**Assumptions**[1]	**Estimated intake (mg/kg-bw per day)**
Environmental media (indirect exposure)		
Air	- based on the limit of detection for 2-methoxyethanol in air in the Canadian multimedia study (5 $\mu g/m^3$) (Conor Pacific Environmental Technologies, 1998) - an average Canadian adult is assumed to weigh 70.9 kg and breathe 16.2 m^3 of air per day (EHD, 1998)	0.0011
Water	- based on the limit of detection for 2-methoxyethanol in water in the Canadian multimedia study (0.6 $\mu g/L$) (Conor Pacific Environmental Technologies, 1998) - an average Canadian adult is assumed to weigh 70.9 kg and consume 1.5 L of tap water per day (EHD, 1998)	0.000 013
Consumer products (direct exposure)		
Nail polish remover	- based on the upper bound of the concentration range of >30–100% of 2-methoxyethanol in nail polish remover - assumes a typical quantity of product used per event for "nail polish & enamel remover" of 3.06 g and a maximum event frequency of 0.29 times per day for users only (U.S. EPA, 1997) - a body weight of 70.9 kg is assumed for an average Canadian adult (EHD, 1998) $\frac{(1)\,(0.29/\text{day})\,(3060\ \text{mg})}{(70.9\ \text{kg})}$	12.5
All-purpose liquid cleaner	**Inhalation** - based on a maximum concentration of 2% 2-methoxyethanol in all-purpose liquid cleaner (Flick, 1986, 1989) - assumes a mass of 35 g is used per event, a 0.47-hour duration of exposure, a room volume of 20 m^3, a breathing rate of 1.3 m^3/hour for an average adult during light-level activity and a frequency of use of 360 days per year (Versar Inc., 1986) - a body weight of 70.9 kg is assumed for an average Canadian adult (EHD, 1998) $\frac{(0.02)\,(35\,000\ \text{mg})\,(0.47\ \text{hours})\,(1.3\ m^3/\text{hour})\,(360/365\ \text{days})}{(20\ m^3)\,(70.9\ \text{kg})}$	0.3

Exposure medium	**Assumptions**[1]	**Estimated intake (mg/kg-bw per day)**
	Dermal - based on a maximum concentration of 2% 2-methoxyethanol in all-purpose liquid cleaner (Flick, 1986, 1989) - assumes an event frequency of 360 days per year, an exposed surface area of 400 cm^2 (both palms), a product density of 1.19 g/cm^3 and a film thickness on the hands of 2.1×10^{-3} cm^2 (Versar Inc., 1986) - a body weight of 70.9 kg is assumed for an average Canadian adult (EHD, 1998) $\frac{(0.02)\,(360/365\text{ days})\,(400\text{ cm}^2)\,(1.19\text{ g/cm}^3)\,(2.1 \times 10^{-3}\text{ cm}^2)\,(1000\text{ mg/g})}{(70.9\text{ kg})}$	0.28
All-purpose spray cleaner	**Inhalation** - based on a maximum concentration of 2% 2-methoxyethanol in all-purpose spray cleaner (Flick, 1986, 1989) - assumes a mass of 76 g is used per event, a 0.47-hour duration of exposure, a room volume of 20 m^3, a breathing rate of 1.3 m^3/hour for an average adult during light-level activity and a frequency of use of 360 days per year (Versar Inc., 1986) - a body weight of 70.9 kg is assumed for an average Canadian adult (EHD, 1998) $\frac{(0.02)\,(76\,000\text{ mg})\,(0.47\text{ hours})\,(1.3\text{ m}^3\text{/hour})\,(360/365\text{ days})}{(20\text{ m}^3)\,(70.9\text{ kg})}$	0.65 [estimated indoor air concentration of 76 mg/m^3]
	Dermal - based on a maximum concentration of 2% 2-methoxyethanol in all-purpose spray cleaner (Flick, 1986, 1989) - assumes an event frequency of 360 days per year, an exposed surface area of 400 cm^2 (both palms), a product density of 0.88 g/cm^3 and a film thickness on the hands of 2.1×10^{-3} cm^2 (Versar Inc., 1986) - a body weight of 70.9 kg is assumed for an average Canadian adult (EHD, 1998) $\frac{(0.02)\,(360/365\text{ days})\,(400\text{ cm}^2)\,(0.88\text{ g/cm}^3)\,(2.1 \times 10^{-3}\text{ cm}^2)\,(1000\text{ mg/g})}{(70.9\text{ kg})}$	0.21

Exposure medium	**Assumptions[1]**	**Estimated intake (mg/kg-bw per day)**
Varnish	**Inhalation** - based on a maximum concentration of 1.1% 2-methoxyethanol in varnish (Versar Inc., 1986) - assumes a mass of 150 g is used per event, a 0.47-hour duration of exposure, a room volume of 125 m^3, a breathing rate of 1.3 m^3/hour for an average adult during light-level activity and a frequency of use of 24 days per year (Versar Inc., 1986) - a body weight of 70.9 kg is assumed for an average Canadian adult (EHD, 1998) $\frac{(0.011)\ (150\,000\ \text{mg})\ (0.47\ \text{hours})\ (1.3\ \text{m}^3/\text{hour})\ (360/365\ \text{days})}{(125\ \text{m}^3)\ (70.9\ \text{kg})}$	0.0075 [estimated indoor air concentration of 13 mg/m^3]
	Dermal - based on a maximum concentration of 1.1% 2-methoxyethanol in varnish (Versar Inc., 1986) - assumes an event frequency of 24 days per year, an exposed surface area of 190 cm^2 (10% of the hands and forearms), a product density of 0.88 g/cm^3 and a film thickness on the hands of 15.88×10^{-3} cm^2 (Versar Inc., 1986) - a body weight of 70.9 kg is assumed for an average Canadian adult (EHD, 1998) $\frac{(0.011)\ (24/365\ \text{days})\ (190\ \text{cm}^2)\ (0.88\ \text{g/cm}^3)\ (15.88 \times 10^{-3}\ \text{cm}^2)\ (1000\ \text{mg/g})}{(70.9\ \text{kg})}$	0.027

[1] For all of the consumer products, it is assumed that 100% of the 2-methoxyethanol is absorbed.

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Canadian Environmental Protection Act, 1999

PRIORITY SUBSTANCES LIST

ASSESSMENT REPORT

2-ETHOXYETHANOL

Environment Canada
Health Canada

August 2000

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LIST OF ACRONYMS AND ABBREVIATIONS

BCF	bioconcentration factor
CAS	Chemical Abstracts Service
CEPA	*Canadian Environmental Protection Act*
CEPA 1999	*Canadian Environmental Protection Act, 1999*
CTV	Critical Toxicity Value
EAA	ethoxyacetic acid
EALD	ethoxyacetaldehyde
EEV	Estimated Exposure Value
ENEV	Estimated No-Effects Value
GWP	Global Warming Potential
HC_5	hazardous concentration for 5% of test species
IC_{50}	inhibitory concentration for 50% of test species
K_{oc}	soil sorption coefficient
K_{ow}	octanol/water partition coefficient
kg-bw	kilogram body weight
LC_{50}	median lethal concentration
LD_{50}	median lethal dose
LOAEL	Lowest-Observed-Adverse-Effect Level
LOEL	Lowest-Observed-Effect Level
NOAEL	No-Observed-Adverse-Effect Level
NOEL	No-Observed-Effect Level
NO_x	nitrogen oxides
NPRI	National Pollutant Release Inventory
ODP	Ozone Depletion Potential
POCP	Photochemical Ozone Creation Potential
PSL	Priority Substances List

Synopsis

2-Ethoxyethanol is not commercially produced in Canada. It is imported for use mainly as a component of formulated products. All environmental releases are reported to be to the atmosphere. Some 2-ethoxyethanol is also sent to landfills and other waste disposal sites.

2-Ethoxyethanol reacts with hydroxyl radicals in the air with a half-life of about 0.2–4 days. Much of the 2-ethoxyethanol released to the atmosphere is predicted to remain in air, but a substantial proportion would partition to water and to soil. 2-Ethoxyethanol is biodegraded in surface water and aerobic soil with an estimated half-life of 1–4 weeks. It is somewhat more persistent under anaerobic conditions. 2-Ethoxyethanol has a very low octanol/water partition coefficient and is therefore not expected to bioaccumulate to any significant degree. There are very few available data on concentrations of 2-ethoxyethanol in the environment in Canada or elsewhere.

Data on toxicity exist for aquatic organisms, including microorganisms, invertebrates and fish. 2-Ethoxyethanol is not very toxic to these organisms; in a number of studies, the LC_{50} was above the highest concentration tested.

Exposure values for air were based on limited Canadian monitoring data. Because of the paucity of environmental monitoring data, exposure values for soil and water were estimated based on fugacity modelling. Estimated environmental concentrations of 2-ethoxyethanol are several orders of magnitude lower than the adverse effects thresholds calculated for sensitive organisms.

2-Ethoxyethanol is not involved in stratospheric ozone depletion and is not an important contributor to climate change or ground-level ozone formation.

2-Ethoxyethanol has consistently induced hematological, reproductive (effects on testes and sperm parameters) and developmental effects in multiple species of experimental animals exposed by various routes. In addition, there is some limited evidence of effects on the blood and reduced sperm production in occupationally exposed human populations. Although monitoring data are very limited, the margins between upper-bounding estimates of exposure to 2-ethoxyethanol in the general environment and conservative effect levels for critical effects are large. However, upper-bounding estimates of exposure to 2-ethoxyethanol through use of some consumer products containing the substance may approach or exceed these conservative effect levels, although the degree of confidence in the estimates of exposure from consumer products is considered to be extremely low.

Based on these considerations, it is concluded that 2-ethoxyethanol is not entering the environment in a quantity or concentration or under conditions that have or may have an immediate or long-term harmful effect on the environment or its biological diversity or that constitute or may constitute a danger to the environment on which life depends. Based on comparison of upper-bounding estimates of exposure in the general environment with

conservative effect levels, it is concluded that 2-ethoxyethanol is not entering the environment in a quantity or concentration or under conditions that constitute or may constitute a danger in Canada to human life or health. Therefore, it is proposed that 2-ethoxyethanol not be considered to be "toxic" as defined in Section 64 of the *Canadian Environmental Protection Act, 1999* (CEPA 1999).

Although 2-ethoxyethanol was not detected in emissions from a range of consumer products in Canada, acquisition of additional more representative information on its use in consumer products in Canada is desirable.

1.0 INTRODUCTION

The *Canadian Environmental Protection Act, 1999* (CEPA 1999) requires the federal Ministers of the Environment and of Health to prepare and publish a Priority Substances List (PSL) that identifies substances, including chemicals, groups of chemicals, effluents and wastes, that may be harmful to the environment or constitute a danger to human health. The Act also requires both Ministers to assess these substances and determine whether they are "toxic" or capable of becoming "toxic" as defined in Section 64 of the Act, which states:

> ...a substance is toxic if it is entering or may enter the environment in a quantity or concentration or under conditions that
> (a) have or may have an immediate or long-term harmful effect on the environment or its biological diversity;
> (b) constitute or may constitute a danger to the environment on which life depends; or
> (c) constitute or may constitute a danger in Canada to human life or health.

Substances that are assessed as "toxic" as defined in Section 64 may be placed on Schedule I of the Act and considered for possible risk management measures, such as regulations, guidelines, pollution prevention plans or codes of practice to control any aspect of their life cycle, from the research and development stage through manufacture, use, storage, transport and ultimate disposal.

Based on initial screening of readily accessible information, the rationale for assessing 2-ethoxyethanol (along with 2-methoxyethanol and 2-butoxyethanol) provided by the Ministers' Expert Advisory Panel on the Second Priority Substances List (Ministers' Expert Advisory Panel, 1995) was as follows:

> Potential sources of exposure to these compounds include releases from various industrial and consumer uses. These compounds are widely used as solvents in paints and protective coatings; in printing inks, industrial solvents and cleaners; in the production of plasticizers; as a de-icer in fuels and automotive brake fluids; and in electronics manufacturing. Effects due to exposure include disorders of the central nervous system, blood system, kidneys and liver in both humans and animals. An assessment is required to determine the presence of these substances in the Canadian environment, exposure and the potential risks to human health.

Descriptions of the approaches to assessment of the effects of Priority Substances on the environment and human health are available in published companion documents.

The document entitled "Environmental Assessments of Priority Substances under the *Canadian Environmental Protection Act*. Guidance Manual Version 1.0 — March 1997" (Environment Canada, 1997a) provides guidance for conducting environmental assessments of Priority Substances in Canada. This document may be purchased from:

Environmental Protection Publications
Environmental Technology Advancement Directorate
Environment Canada
Ottawa, Ontario
K1A 0H3

It is also available on the Commercial Chemicals Evaluation Branch web site at www.ec.gc.ca/cceb1/eng/psap.htm under the heading "Technical Guidance Manual." It should be noted that the approach outlined therein has evolved to incorporate recent developments in risk assessment methodology, which will be addressed in future releases of the guidance manual for environmental assessments of Priority Substances.

The search strategies employed in the identification of data relevant to the assessment of entry, environmental fate and exposure, and potential effects on the environment (prior to October 1999) are presented in Appendix A. Review articles were consulted where appropriate. However, all original studies that form the basis for determining whether 2-ethoxyethanol is "toxic" under Paragraphs 64(a) or 64(b) of CEPA 1999 have been critically evaluated by staff of Environment Canada.

The approach to assessment of effects on human health is outlined in the following publication of the Environmental Health Directorate of Health Canada: "*Canadian Environmental Protection Act* — Human Health Risk Assessment for Priority Substances" (Health Canada, 1994), copies of which are available from:

Environmental Health Centre
Room 104
Health Canada
Tunney's Pasture
Ottawa, Ontario
K1A 0L2

or on the Environmental Health Directorate publications web site (www.hc-sc.gc.ca/ehp/ehd/catalogue/bch.htm). The approach is also described in an article published in the *Journal of Environmental Science and Health — Environmental Carcinogenesis & Ecotoxicology Reviews* (Meek *et al*., 1994). It should be noted that the approach outlined therein has evolved to incorporate recent developments in risk assessment methodology, which are described on the Environmental Substances Division web site (www.hc-sc.gc.ca/ehp/ehd/bch/env_contaminants/psap/psap.htm) and which will be addressed in future releases of the approach paper for the assessment of effects on human health.

The approach to assessment of 2-ethoxyethanol is necessarily restricted because of the extremely limited data upon which to base estimates of population exposure. In this assessment, available information relevant to characterization of health hazards was critically evaluated to ascertain critical effects; lowest effect levels for these effects from studies in experimental animals or exposed human populations are compared with worst-case or bounding estimates of exposure. The adequacy of these rather crude margins of exposure is considered in relation to intake from various sources, including environmental media and consumer products, estimated on the basis of the limited available Canadian data. This approach has been adopted as a basis to determine whether additional refinement is required in considering priority of investigation of options to reduce exposure in the general environment under CEPA 1999. On this basis, areas where additional information may be required to better characterize risk of the general population in Canada from all sources have also been identified.

Data relevant to assessment of population exposure and potential effects on human health were identified on the basis of a review prepared in 1996 by BIBRA Toxicology International as well as through literature searches, the strategies for which are described in Appendix A (prior to January 2000). All original studies that form the basis for determining whether 2-ethoxyethanol is "toxic" under Paragraph 64(c) of CEPA 1999 have been critically evaluated by staff of Health Canada.

Sections of the Assessment Report related to the environmental assessment of 2-ethoxyethanol and the environmental Supporting Document (Environment Canada, 1999) were prepared or reviewed by the members of the Environmental Resource Group, established by Environment Canada to support the environmental assessment:

D. Boersma, Environment Canada
R. Breton, Environment Canada
P. Cureton, Environment Canada
N. Davidson, Environment Canada
R. Desjardins, Environment Canada
L. Hamel, Union Carbide Canada Inc.
B. Lee, Environment Canada
S. Lewis, Chemical Manufacturers' Association
B. Sebastien, Environment Canada
K. Taylor, Environment Canada (lead for the environmental assessment)

Sections of the Assessment Report relevant to the environmental assessment and the environmental Supporting Document (Environment Canada, 1999) were also reviewed by C. Staples of Assessment Technologies Inc.

Sections of the Assessment Report related to human health and the background supporting documentation were prepared by the following staff of Health Canada:

K. Hughes
M.E. Meek

L. Turner

Comments on the adequacy of data coverage in the sections of the supporting documentation related to health effects were provided in a written review by J.B. Knaak of Oxychem (retired).

The health-related sections of the Assessment Report were reviewed and approved by the Health Protection Branch Risk Management meeting.

The entire Assessment Report was reviewed and approved by the Environment Canada/Health Canada CEPA Management Committee.

The text of the Assessment Report has been structured to address environmental effects initially (relevant to determination of "toxic" under Paragraphs 64(a) and (b)), followed by effects on human health (relevant to determination of "toxic" under Paragraph 64(c)).

Copies of this Assessment Report are available upon request from:

Inquiry Centre
Environment Canada
Main Floor, Place Vincent Massey
351 St. Joseph Blvd.
Hull, Quebec
K1A 0H3

or on the Internet at:

www.ec.gc.ca/cceb1/eng/public/index_e.html

Unpublished supporting documentation, which presents additional information, is available upon request from:

Commercial Chemicals Evaluation Branch
Environment Canada
14th Floor, Place Vincent Massey
351 St. Joseph Blvd.
Hull, Quebec
K1A 0H3

or

Environmental Health Centre
Room 104
Health Canada
Tunney's Pasture
Ottawa, Ontario
K1A 0L2

2.0 SUMMARY OF INFORMATION CRITICAL TO ASSESSMENT OF "TOXIC" UNDER CEPA 1999

2.1 Identity and physical/chemical properties[1]

2-Ethoxyethanol, one of the class of substances referred to as glycol ethers, has the empirical molecular formula $C_4H_{10}O_2$, the structural formula $CH_3CH_2OCH_2CH_2OH$ and a molecular weight of 90.12. Its Chemical Abstracts Service (CAS) registry number is 110-80-5. 2-Ethoxyethanol is a colourless liquid with an estimated water solubility of 300 000 mg/L[2] (DMER and AEL, 1996), a log octanol/water partition coefficient (K_{ow}) of –0.32 (Hansch *et al.*, 1995), a vapour pressure of 710 Pa (Riddick *et al.*, 1986) and a calculated Henry's law constant of 0.213 $Pa{\cdot}m^3/mol$ (DMER and AEL, 1996).

Synonyms for 2-ethoxyethanol include 2-ethoxy-1-ethanol, ethylene glycol monoethyl ether and ethyl Cellosolve.

2.2 Entry characterization

2.2.1 Production, importation and uses

2-Ethoxyethanol was not produced in Canada in 1995 or 1996, according to data reported to Environment Canada by 14 companies in a survey carried out under the authority of Section 16 of the *Canadian Environmental Protection Act, 1988* (CEPA) (Environment Canada, 1997b). According to these data, importation of 2-ethoxyethanol totalled 4.7 kilotonnes in 1995 and 3.0 kilotonnes in 1996. There was no export of 2-ethoxyethanol in 1995, and 2.3 tonnes were exported in 1996.

2-Ethoxyethanol has been used in paints, coatings, inks, cleaners, polishes, brake fluids and jet fuels and has been widely used as a solvent, chemical intermediate and solvent coupler of mixtures and water-based formulations (Stemmler *et al.*, 1997). Data reported to Environment Canada in the survey conducted under the authority of Section 16 of CEPA indicated that 68.2 and 42.8 tonnes of 2-ethoxyethanol were used in Canada in 1995 and 1996, respectively, mainly as a component of formulated products (Environment Canada, 1997b). 2-Ethoxyethanol is present as a minor ingredient (<1.25%) in 26 Canadian registered pest control products (wood preservatives) (Ballantine, 1997; Health Canada, 1998a).

---

[1] See the environmental Supporting Document (Environment Canada, 1999) for a more complete listing of ranges of values reported and criteria for selection of physical and chemical properties.

[2] This estimated value was based on reported values for structurally similar or homologous compounds (DMER and AEL, 1996).

2.2.2 Sources and releases

2.2.2.1 Natural sources

2-Ethoxyethanol has not been reported to occur as a natural product (U.S. EPA, 1986; WHO, 1990). There are no known reactions that would lead to the *in situ* production of glycol ethers in the atmosphere (Rogozen *et al.*, 1987).

2.2.2.2 Anthropogenic sources

Total on-site environmental releases of 2-ethoxyethanol reported to the National Pollutant Release Inventory (NPRI) in 1994 amounted to 2.36 tonnes. Most of this (at least 81%) was released into the atmosphere from four facilities (producing plastics and synthetic resins, paint and varnish, petroleum products and printing ink) in Quebec (NPRI, 2000). (Facilities with more than 10 full-time staff and that use or manufacture more than 10 tonnes of substances on the NPRI are required by law to report to Environment Canada.)

In 1995, total on-site environmental releases of 2-ethoxyethanol reported to the NPRI amounted to 8.1 tonnes (NPRI, 2000). Almost all of this was released into the atmosphere as emissions from storage from one facility (plastics manufacturing) in Ontario.

In 1996, total on-site environmental releases of 2-ethoxyethanol were 0.20 tonnes, released about equally from two facilities (producing motor vehicle stampings and industrial and household chemicals) in Ontario and Quebec (NPRI, 2000).

Releases reported to date for 1997 totalled 9.32 tonnes, from two printing ink industries in Ontario and Quebec (NPRI, 2000).

According to data reported under the CEPA Section 16 survey (with different reporting requirements from the NPRI), 5.8 tonnes of 2-ethoxyethanol were released to landfills in 1996, while 3.9 tonnes were released as waste and 0.9 tonnes were released to air from several facilities in Ontario and Quebec (Environment Canada, 1997b). (Industries surveyed by Environment Canada with commercial activities involving more than 1000 kg of 2-ethoxyethanol were required to supply data on uses and releases and other relevant information.)

The Canadian Chemical Producers' Association (1999a) reported total environmental emissions of 2-ethoxyethanol of 0.3, 0.015, 0.015 and 0.013 tonnes from member companies in 1992, 1993, 1994 and 1995, respectively, all of which were released to air by a single company. Reported emissions fell to 0 tonnes in 1996 (Canadian Chemical Producers' Association, 1999a), totalied 0.003 tonnes in 1997 and returned to 0 tonnes in 1998 (Canadian Chemical Producers' Association, 1999b).

2.3 Exposure characterization

2.3.1 Environmental fate

2.3.1.1 Air

An atmospheric half-life of 9.8 hours was determined in a smog chamber with irradiation at a 2-ethoxyethanol:NO_x ratio of 2:1 (Joshi *et al*., 1982). A half-life of about 4 days was calculated for the reaction of 2-ethoxyethanol with atmospheric hydroxyl radicals, assuming an ambient concentration of hydroxyl radicals of 10^6 molecules/cm^3 (U.S. EPA, 1985). This calculation was based on the rate constant in water of 1×10^9 L/mol per second (Anbar and Neta, 1967), converted to a gas-phase reaction by the method of Guesten *et al*. (1981). Howard *et al*. (1991) estimated a half-life of 2-ethoxyethanol in air of 5.35–53.5 hours, based on reaction with hydroxyl radicals.

2.3.1.2 Water

Howard *et al*. (1991) estimated half-lives of 2-ethoxyethanol of 168–672 hours and 336–1344 hours in surface water and groundwater, respectively, based on unacclimated aerobic biodegradation.

2.3.1.3 Soils

A soil sorption coefficient (K_{oc}) of 113 was calculated for 2-ethoxyethanol using the method of Sabljic (1984), indicating moderate mobility in soil (U.S. EPA, 1985). Retention values for 2-ethoxyethanol of 21 New Zealand and Fijian soils ranged from 8 to 178 mg/g; these values were well correlated with the cation exchange capacity and a number of measures of moisture content of these soils (Churchman and Burke, 1991).

There is little information available on the biodegradation of 2-ethoxyethanol in soil. Howard *et al*. (1991) estimated a half-life of 2-ethoxythanol in soil of 168–672 hours, based on unacclimated aerobic biodegradation. 2-Ethoxyethanol underwent biooxidation to 2-ethoxyacetic acid (EAA) by the soil bacterium, *Alcaligenes* MC11, for which 2-ethoxyethanol was a source of carbon (Harada and Nagashima, 1975). *Pseudomonas* sp. 4-5-3, *Xanthobacter autotrophicus* EC1-2-1 and a bacterium identified only as “strain MC2-2-1” could also use 2-ethoxyethanol as a source of carbon for aerobic growth (Kawai, 1995).

2.3.1.4 Biota

A bioconcentration factor (BCF) of 0.5 was estimated for 2-ethoxyethanol, based on a log K_{ow} of -0.10 and using the equation proposed by Lyman *et al*. (1982) (i.e., $\log BCF = 0.76 \log K_{ow} - 0.23$)

(U.S. EPA, 1985). Bioaccumulation of 2-ethoxyethanol in aquatic organisms would therefore not be significant.

2.3.1.5 Environmental distribution

Because of the high water solubility of 2-ethoxyethanol and its low log K_{ow}, physical adsorption to suspended solids and sediments should not be significant (U.S. EPA, 1985).

The environmental partitioning of 2-ethoxyethanol when released into air, water or soil was estimated by a Level III fugacity model (DMER and AEL, 1996). Values for input parameters were as follows: molecular weight, 90.1 g/mol; vapour pressure, 710 Pa; water solubility, 300 000 mg/L; log K_{ow}, –0.32; Henry's law constant, 0.213 Pa·m^3/mol; half-life[3] in air, 55 hours; half-life in water, 550 hours; half-life in soil, 550 hours; and half-life in sediment, 1700 hours. Modelling was based upon an assumed emission rate of 1000 kg/hour, although the emission rate used would not affect the estimated percent distribution. If 2-ethoxyethanol is emitted into air, EQC (Equilibrium Criterion) Level III fugacity modelling predicts that about 50% would be present in air, while approximately 25% would be present in soil and about 25% in water. If 2-ethoxyethanol is emitted into water, more than 99% would be present in water. If 2-ethoxyethanol is released to soil, about 75% would be present in the soil, while approximately 25% would be present in water (DMER and AEL, 1996).

2.3.2 Environmental concentrations

Few data on levels of 2-ethoxyethanol in the environment have been identified for Canada or elsewhere. One study was conducted to determine concentrations of 2-ethoxyethanol in multiple media in Canada to which humans are exposed, including drinking water and indoor and outdoor air (Conor Pacific Environmental Technologies, 1998), as outlined below in Section 2.3.2.1. Additional data on levels of 2-ethoxyethanol in specific media are presented in the subsequent sections where identified.

2.3.2.1 Multimedia exposure study

In a multimedia exposure study, exposure to a number of volatile organic chemicals was measured for 50 participants across Canada in 1997 (Conor Pacific Environmental Technologies, 1998). Thirty-five participants were randomly selected from the Greater Toronto area in Ontario, six from Queens Subdivision in Nova Scotia and nine from Edmonton, Alberta. For each participant, samples of drinking water, beverages and indoor, outdoor and personal air were collected over a 24-hour period; however, samples of food were not analysed for 2-ethoxyethanol. While confidence in the results of this survey was low (see Section 3.3.4), the concentration of 2-ethoxyethanol was below the method detection limit (0.05 µg/L) in all samples of drinking water. Similarly, it was not detected (detection limit 3.6 µg/m^3) in any samples of indoor, outdoor or personal air. 2-Ethoxyethanol was not detected in composite beverage samples (method detection limit 3.3 µg/L).

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[3] For each environmental compartment, DMER and AEL (1996) use a series of ranges of half-life times (<10 hours, 10–30 hours, 30–100 hours, etc.), and the half-life of the particular substance is assigned to the appropriate range, based on a consideration of available persistence data. The geometric mean of this range is then used as an input parameter for the fugacity model. For example, the atmospheric half-life of 2-ethoxyethanol in air is judged to be between 30 and 100 hours. The geometric mean of this range, 55 hours, is used as an input parameter in the model. Conservative values for persistence were selected, i.e., longer rather than shorter half-lives, to ensure that persistence is not underestimated.

2.3.2.2 Ambient air

In the Windsor Air Quality Study, the concentrations of 2-ethoxyethanol in 24 samples of ambient air collected in the vicinity of an automotive plant and 7 samples in downtown Windsor (OMEE, 1994) were measured. Concentrations of 2-ethoxyethanol were less than the limit of detection (0.81 µg/m^3) in all the samples collected in downtown Windsor. Of the 24 samples collected at the automotive plant, concentrations of 2-ethoxyethanol were above the limits of detection (which ranged from 0.18 to 0.34 µg/m^3) in 16 (over 66%); the mean value for these samples was 0.43 µg/m^3 when concentrations in samples where 2-ethoxyethanol was not detected were assumed to be equivalent to one-half the limit of detection (maximum 0.86 µg/m^3). The authors stated that the probable source of 2-ethoxyethanol in ambient air samples downwind of the plant was from paints and lacquers in which 2-ethoxyethanol is used as a solvent. In all of the samples from downtown Windsor or in the vicinity of the automotive plant, concentrations of 2-ethoxyethyl acetate, the acetate moiety of 2-ethoxyethanol, were below the limits of detection (range 0.55–2.9 µg/m^3).

2-Ethoxyethanol was not detected in samples of ambient air collected at six locations in the United States in 1984–1985 (limit of detection 0.25 µg/m^3) (Sheldon *et al.*, 1988).

2.3.2.3 Indoor air

In northern Italy, six indoor air samples collected from homes in 1983–1984 contained 2-ethoxyethanol concentrations of up to 60 µg/m^3 (De Bortoli *et al.*, 1986). 2-Ethoxyethanol was detected at concentrations of up to 18.3 µg/m^3 in indoor air samples collected in new buildings (hospital, office, nursing home) in the United States. In older buildings (office, nursing home, school), concentrations were lower (i.e., up to 4.15 µg/m^3) (Sheldon *et al.*, 1988).

2.3.2.4 Surface water

Samples of water from a polluted river in Japan contained 250–1200 µg 2-ethoxyethanol/L (Yasuhara *et al.*, 1981).

2.3.2.5 Consumer products

Glycol ethers are used as solvents in a number of consumer products, including paints, paint thinners and cleaning products. In Canada, glycol ethers, including 2-ethoxyethanol and its acetate,[4] are not regulated in consumer products (Health Canada, 1998b). According to Material Safety Data Sheets obtained from a paint production company in British Columbia (General Paint Ltd., 1997), 2-ethoxyethyl acetate comprises up to 5% in latex paints and up to 60% in paint thinners. 2-Ethoxyethanol is a component of 26 wood preservatives registered for use in Canada (<1.25%) (Ballantine, 1997; Health Canada, 1998a). Glycol ethers, including 2-ethoxyethanol, are not registered for use as active ingredients in therapeutic products used in Canada (Health Canada, 1998c). Of the cosmetic products registered for use in Canada, one nail polish contained 2-ethoxyethanol in the range of 0.3–1% (Health Canada, 1998d). (The *Food and Drugs Act* stipulates that manufacturers and importers of new cosmetic products are required to notify Health Canada concerning the ingredients.) However, 2-ethoxyethanol was not detected in the emissions of 13 consumer products, including window cleaners, all-purpose cleaners, paints, nail polish removers and hair dye, purchased in the Ottawa, Ontario, area (Cao, 1999). (These products were selected on the basis of other data presented here that suggested that 2-ethoxyethanol was present in similar products.)

In the United States, concentrations of 2-ethoxyethanol up to 5% were reported in various consumer products, including hard surface cleaners, floor polishes and windshield washing fluid (Flick, 1986). However, in a more recent listing of ingredients in "advanced" cleaning product formulations, none of the products contained 2-ethoxyethanol or 2-ethoxyethyl acetate (Flick, 1994). (It should be noted that these data were submitted voluntarily by numerous companies and other organizations and may not represent a comprehensive list of formulations of consumer products available in the United States.) Additional data on emissions of 2-ethoxyethanol and its acetate from several consumer products tested in the United States are presented in Table 1 (although no information was provided in the secondary account regarding the number of products examined). A European patent application for hair dye lists a 2-ethoxyethanol concentration of 12% (Cotteret, 1995). According to the 1993 Products Register in Sweden (reporting of the composition of products manufactured or imported in Sweden is mandatory), 2-ethoxyethanol and its acetate were ingredients in 137 and 170 products, totalling 105–242 and 172–270 tonnes/year, respectively, of pure substance (Johanson and Rick, 1996).

2.3.2.6 Fugacity modelling

Environmental concentrations of 2-ethoxyethanol were estimated by ChemCAN4 modelling. This model is a Level III fugacity-based regional model developed to estimate the environmental fate of chemicals in

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[4] The acetate moiety of 2-ethoxyethanol, 2-ethoxyethyl acetate, is often used in consumer product formulations. Since the acetate is rapidly converted to the parent 2-ethoxyethanol in the body, data on the presence of the acetate in consumer products are considered relevant to estimation of population exposure to 2-ethoxyethanol.

Canada. ChemCAN calculates the distribution of chemicals in environmental media, the transport and transformation process rates, and average concentrations in any of 24 regions or ecozones of Canada. The highest reported recent release of 2-ethoxyethanol in Canada is 8 tonnes/year, released into the air by one facility in southern Ontario in 1995 (NPRI, 1998). "Ontario – Mixed Wood Plain" was therefore selected as the geographic region for ChemCAN modelling of 2-ethoxyethanol. The input rate was 0.913 kg 2-ethoxyethanol/hour, all to the atmosphere. Chemical input values were as follows: molecular weight, 90.1 g/mol; vapour pressure, 710 Pa; water solubility, 300 000 mg/L; log K_{ow}, –0.32; Henry's law constant, 0.213 Pa·m^3/mol; half-life in air, 55 hours; half-life in water, 550 hours; half-life in soil, 550 hours; and half-life in sediment, 1700 hours. For Ontario – Mixed Wood Plain, environmental characteristics were as follows: total surface area, 169 000 km^2; percentage covered by water, 43.8%; average air height, 2 km; average water depth, 20 m; average soil depth, 10 cm; residence time in air, 1.71 days; residence time in water, 618 days; environmental temperature, 7.4°C.

Environmental concentrations of 2-ethoxyethanol in southern Ontario predicted by ChemCAN4 modelling are as follows: 6.9×10^{-2} ng/m^3 in air; 2.2×10^{-5} µg/L in water; 4.15×10^{-4} ng/g dry weight in soil; and 1.05×10^{-5} ng/g dry weight in sediments. The ChemCAN model estimates average concentrations throughout the region; therefore, actual concentrations in the vicinity of releases will be higher than those estimated by the model.

2.4 Effects characterization

2.4.1 Ecotoxicology

2.4.1.1 Terrestrial organisms

No information on the effects of 2-ethoxyethanol on wildlife was identified. Data for experimental animals pertinent to the human health assessment are presented in Section 2.4.3. From the results of inhalation studies presented in this section, the species that were most sensitive to airborne 2-ethoxyethanol were rats and rabbits. Developmental effects (skeletal variations) were induced in rats exposed to 2-ethoxyethanol at a concentration of 50 ppm (184 mg/m^3) for 10 days (Doe, 1984). Developmental toxicity (reduced mean number of implantations and number of live fetuses) was also observed in Dutch rabbits exposed to 2-ethoxyethanol in air at a concentration of 50 ppm (184 mg/m^3) (Tinston, 1983a).

2.4.1.2 Aquatic organisms

Data on chronic toxicity have been identified only for protozoans, algae and hydra. The most sensitive organisms were microbial populations in waste stabilization ponds, with approximately a 40% inhibition of respirometric activity (i.e., changes in total organic carbon, chemical oxygen demand and 2-ethoxyethanol concentration) at 1 000 000 µg/L in a 5-day study (Davis *et al.*, 1989). Data on acute toxicity have been reported for invertebrates and fish, although in many studies the LC_{50} for 2-

ethoxyethanol was above the highest concentration tested. For example, the 24-hour LC_{50} for goldfish (*Carassius auratus*) was >5 000 000 μg/L (Bridie *et al.*, 1979). Hermens *et al.* (1984) reported a 48-hour IC_{50} of 7 660 000 μg/L for *Daphnia magna*.

2.4.2 Abiotic atmospheric effects

Worst-case calculations were made to determine if 2-ethoxyethanol has the potential to contribute to depletion of stratospheric ozone, ground-level ozone formation or climate change (Bunce, 1996).

The Ozone Depletion Potential (ODP) is 0, as 2-ethoxyethanol is not a halogenated compound.

The Photochemical Ozone Creation Potential (POCP) was estimated to be 73 (relative to the reference compound ethene, which has a POCP of 100), based on the following formula:

$$\mathrm{POCP} = (k_{\text{2-ethoxyethanol}}/k_{\text{ethene}}) \times (M_{\text{ethene}}/M_{\text{2-ethoxyethanol}}) \times 100$$

where:

- $k_{\text{2-ethoxyethanol}}$ is the rate constant for the reaction of 2-ethoxyethanol with OH radicals (2.0×10^{-11} cm^3/mol per second),
- k_{ethene} is the rate constant for the reaction of ethene with OH radicals (8.5×10^{-12} cm^3/mol per second),
- M_{ethene} is the molecular weight of ethene (28.1 g/mol), and
- $M_{\text{2-ethoxyethanol}}$ is the molecular weight of 2-ethoxyethanol (90 g/mol).

The Global Warming Potential (GWP) was calculated to be 5.1×10^{-5} (relative to the reference compound CFC-11, which has a GWP of 1), based on the following formula:

$$\mathrm{GWP} = (t_{\text{2-ethoxyethanol}}/t_{\text{CFC-11}}) \times (M_{\text{CFC-11}}/M_{\text{2-ethoxyethanol}}) \times (S_{\text{2-ethoxyethanol}}/S_{\text{CFC-11}})$$

where:

- $t_{\text{2-ethoxyethanol}}$ is the lifetime of 2-ethoxyethanol (0.002 years),
- $t_{\text{CFC-11}}$ is the lifetime of CFC-11 (60 years),
- $M_{\text{CFC-11}}$ is the molecular weight of CFC-11 (137.5 g/mol),
- $M_{\text{2-ethoxyethanol}}$ is the molecular weight of 2-ethoxyethanol (90 g/mol),
- $S_{\text{2-ethoxyethanol}}$ is the infrared absorption strength of 2-ethoxyethanol (2389/cm^2 per atmosphere, default), and
- $S_{\text{CFC-11}}$ is the infrared absorption strength of CFC-11 (2389/cm^2 per atmosphere).

These figures suggest that 2-ethoxyethanol does not contribute to stratospheric ozone depletion, its potential contribution to climate change is negligible and its potential contribution to ground-level ozone formation is moderate. The magnitude of these effects would depend on the concentration of 2-

ethoxyethanol in the atmosphere, and concentrations of the substance in air in Canada are estimated to be very low. The contribution of 2-ethoxyethanol to ozone formation is therefore considered negligible compared with those of other more abundant smog-forming substances, such as the reference compound, ethene (Bunce, 1996).

2.4.3 Experimental animals and in vitro

In view of the limited objective of this assessment relative to dose–response (i.e., characterization of lowest effect levels only for critical effects), presentation of data on health effects associated with 2-ethoxyethanol is limited to an overview of the nature of the effects, with emphasis on the lowest identified effect levels from repeated-exposure studies relevant to characterization of margins between estimates of population exposure and levels causing toxic effects; detailed descriptions of study protocols and results are included in the supporting documentation.

2.4.3.1 Kinetics and metabolism

2-Ethoxyethanol is rapidly absorbed in humans and experimental animals exposed via ingestion, inhalation or dermal contact. In humans and laboratory animals, 2-ethoxyethanol is oxidized via alcohol dehydrogenases to the intermediate ethoxyacetaldehyde (EALD) and then rapidly converted via aldehyde dehydrogenases to EAA, the principal and putatively active metabolite, which is eliminated primarily in the urine. In rats, EAA may be conjugated with glycine or be O-deethylated and then further metabolized to carbon dioxide. A secondary pathway in rodents involves microsomal P450 mixed-function oxidases, with deethylation producing acetaldehyde and ethylene glycol.

Although little information is available regarding interspecies differences in the toxicokinetics and metabolism of 2-ethoxyethanol, there is some indication that humans may absorb the substance to a greater extent than do rats (the species most extensively investigated) (Groeseneken *et al.*, 1986, 1987). In addition, although relevant data are very limited, 2-ethoxyethanol may be converted to EAA at a greater rate in humans than in rats, with subsequent renal clearance of the metabolite being slower in humans (Groeseneken *et al.*, 1988); thus, the putatively active metabolite may be present in the blood of humans at higher levels and for longer durations than in rats.

The acetate moiety of 2-ethoxyethanol, 2-ethoxyethyl acetate, which is commonly used in occupational and residential environments, is rapidly hydrolysed to 2-ethoxyethanol via esterases in several tissues in the body (Stott and McKenna, 1985). (For this reason, data on the toxicity of 2-ethoxyethyl acetate have been included in this assessment.)

2.4.3.2 Acute toxicity

2-Ethoxyethanol is of low to moderate acute toxicity in experimental animals following oral exposure, with reported LD_{50}s in various species ranging from 1400 to 5490 mg/kg-bw (Laug *et al.*, 1939; Smyth *et al.*, 1941; Carpenter, 1947; Carpenter *et al.*, 1956; Stenger *et al.*, 1971; Truhaut *et al.*, 1979; Krasavage and Terhaar, 1981; Dow Chemical Company, unpublished data, cited in Clayton and Clayton, 1982; Cheever *et al.*, 1984). However, it is considered to be of low toxicity only following inhalation or dermal exposure, with LC_{50}s (7 or 8 hours) in rats and mice of 1500–2000 ppm (5520–7360 mg/m^3) (Werner *et al.*, 1943a; Pozzani *et al.*, 1959; Shell, unpublished data, cited in Tyl *et al.*, 1988) and dermal LD_{50}s of 3314–3920 mg/kg-bw (covered application for 24 hours) in rabbits (Carpenter *et al.*, 1956; Krasavage and Terhaar, 1981; Daughtrey *et al.*, 1984). Target sites of 2-ethoxyethanol-induced acute toxicity include the hematopoietic system, liver, kidneys and stomach. 2-Ethoxyethanol and its acetate did not induce skin sensitization and have only low potential for irritation of skin and eyes (Werner *et al.*, 1943b; Carpenter and Smyth, 1946; Truhaut *et al.*, 1979; Krasavage and Terhaar, 1981; Barbee *et al.*, 1984; Daughtrey *et al.*, 1984; Kennah *et al.*, 1989; Zissu, 1995).

2.4.3.3 Short-term toxicity

2.4.3.3.1 Oral

Based on the few short-term oral studies available, the testes appear to be sensitive target organs in rats, mice and dogs, with histopathological effects (degeneration or atrophy) and/or decreased weights being observed in rats, mice and dogs following repeated doses of 2-ethoxyethanol as low as 919 mg/kg-bw per day (in drinking water), 1000 mg/kg-bw per day (by gavage) and 186 mg/kg-bw per day (in capsules), respectively (Stenger *et al.*, 1971; Nagano *et al.*, 1979, 1984; NTP, 1993). 2-Ethoxyethyl acetate induced similar effects in the testes at gavage doses of 1000 mg/kg-bw per day or more in mice (Nagano *et al.*, 1979, 1984). Reductions in relative thymus weights were also observed in rats administered 357 mg/kg-bw per day or more in drinking water (i.e., doses lower than those that induced testicular effects); no effects on the thymus were observed in mice exposed to much higher doses (NTP, 1993). Hematological effects, consisting of reduced white blood cell counts and packed cell volume, were also observed in mice exposed to 2000 mg/kg-bw per day or more of 2-ethoxyethanol or the acetate by gavage (Nagano *et al.*, 1979, 1984). In the only other short-term oral study in which hematological parameters were investigated, there were slight dose-related decreases in hemoglobin and hematocrit levels in dogs administered 50–200 µL/kg-bw per day (46–186 mg/kg-bw per day) of 2-ethoxyethanol in gelatin capsules for 13 weeks (significance not reported) (Stenger *et al.*, 1971).

2.4.3.3.2 Inhalation

Available data on the toxicity of 2-ethoxyethanol or 2-ethoxyethyl acetate following short-term exposure via inhalation are limited to studies designed primarily to investigate developmental toxicity and two early limited studies in small groups of dogs. Doe (1984) reported changes in red blood cell parameters in pregnant rats exposed to 250 ppm (920 mg/m^3) 2-ethoxyethanol for 10 days, while no effects on the blood were observed at 50 ppm (184 mg/m^3). Similarly, alterations in hematological parameters (red blood cells, white blood cells and platelets) were observed in pregnant rats exposed to

100 ppm or more of 2-ethoxyethyl acetate (equivalent to 368 mg 2-ethoxyethanol/m^3) (Tyl *et al.*, 1988). In studies in rabbits, no effects on the blood were noted in pregnant females exposed to up to 175 ppm (644 mg/m^3) 2-ethoxyethanol, while a reduction in hemoglobin concentration was observed only following exposure to the highest concentration of 2-ethoxyethyl acetate tested (i.e., 400 ppm, equivalent to 1473 mg 2-ethoxyethanol/m^3) (Doe, 1984).

Alterations in hematological parameters characteristic of anemia (i.e., effects on red blood cells) and an increase in calcium oxalate crystals in the urine were observed in dogs exposed to 840 ppm (3091 mg/m^3) 2-ethoxyethanol vapour for 12 weeks (Werner, 1943b), although no such effects were noted in dogs exposed to 600 ppm 2-ethoxyethyl acetate vapour (equivalent to 2210 mg 2-ethoxyethanol/m^3) for 6 months (Carpenter, 1947). No histopathological changes were observed in the limited range of organs examined in either study.

2.4.3.4 Subchronic toxicity

2.4.3.4.1 Oral

In the identified subchronic studies in which rats were administered 2-ethoxyethanol by the oral route, the critical targets were the male reproductive organs and the blood. Testicular degeneration was observed in the testes of male F344/N rats administered 2-ethoxyethanol in drinking water for 13 weeks at concentrations equivalent to doses of 400 mg/kg-bw per day or more, while atrophy of the prostate gland was observed at doses of 205 mg/kg-bw per day or more; the severity of these lesions increased with dose. Concentrations of spermatogonia and sperm were also significantly lower in rats administered 205 mg/kg-bw per day or more of 2-ethoxyethanol. In males, signs of mild anemia (reduced red blood cell count and hemoglobin concentration), which was characterized as macrocytic (increased mean cell volume), hypochromic (decreased mean cell hemoglobin concentration) and poorly regenerative, were observed at 792 mg/kg-bw per day and above as early as 1 week after initiation of exposure. The severity of the anemia increased with duration of exposure and was described as marked to moderate after 3 and 13 weeks. Mild thrombocytopenia and leukopenia were also present in males exposed to 400 mg/kg-bw per day or more after 1 week of exposure; however, the thrombocytopenia appeared to be reversible, based on the lack of significant reduction in platelet count, while leukopenia was judged to be moderate after 13 weeks. Female rats also exhibited mild anemia (again characterized as macrocytic, hypochromic and poorly regenerative) after 1 week of exposure to 2-ethoxyethanol, with some parameters being affected at doses as low as 247 mg/kg-bw per day, as well as moderate to marked thrombocytopenia and moderate leukopenia. After 3 and 13 weeks of exposure, the severity of the anemia was considered to have progressed to moderate and was accompanied by moderate thrombocytopenia and marked leukopenia, which progressed to marked leukocytosis. Increased hematopoiesis and hemosiderin pigmentation of the spleen and liver were also noted, but were considered secondary to hematological effects. Alterations in clinical chemistry parameters indicative of general toxicity or liver dysfunction were noted in males and females at • 205 and • 466 mg/kg-bw per day, respectively. Based on effects on the thymus, testes, prostate gland and blood, the authors (NTP,

1993) considered the Lowest-Observed-Adverse-Effect Level (LOAEL) in male rats to be 205 mg/kg-bw per day (with a No-Observed-Adverse-Effect Level [NOAEL] of 109 mg/kg-bw per day). The authors considered the NOAEL in female rats to be 466 mg/kg-bw per day; however, in view of the observation of thrombocytopenia at all doses, 122 mg/kg-bw per day could be considered to be the Lowest-Observed-Effect Level (LOEL) in females (although the effect on platelet count appeared to have ameliorated somewhat at this exposure level), with numerous other parameters being significantly different from controls at the next dose.

A similar profile of effects was observed in other subchronic oral studies in different strains of rats. Hematological effects consistent with anemia as well as alterations in white blood cell parameters were observed in rats (strain CR,COBS,CD,BR) administered 900 mg/kg-bw per day of 2-ethoxyethanol by gavage for 6 weeks (Krasavage and Vlaovic, 1982). Reduced hemoglobin and hematocrit were also reported in Wistar rats exposed for 13 weeks to 2-ethoxyethanol by gavage (100 µL/kg-bw per day [93 mg/kg-bw per day] for 59 days followed by exposure to 400 µL/kg-bw per day [372 mg/kg-bw per day] for 30 days) (Stenger *et al.*, 1971). Hemosiderin pigmentation was noted in the spleen of both strains of rats, with the lowest effect level being 186 mg/kg-bw per day in Wistar rats. Effects on male reproductive organs (including reduced testicular weights, atrophy and degeneration) and on sperm parameters (degenerated spermatozoa and hypospermia) were also observed in these strains of rats at doses of 450 mg/kg-bw per day (the lowest dose tested) and above for 6 weeks (Krasavage and Vlaovic, 1982) or 200 µL/kg-bw per day (186 mg/kg-bw per day) and above for 13 weeks, but not at 100 µL/kg-bw per day (93 mg/kg-bw per day) (considered to be the No-Observed-Effect Level [NOEL]) (Stenger *et al.*, 1971). Histopathological changes in the stomach and bone marrow were also noted at 450 mg/kg-bw per day or higher (Krasavage and Vlaovic, 1982).

Data on the effects in mice following subchronic oral exposure to 2-ethoxyethanol are limited to a single study in which B6C3F$_1$ mice were exposed via drinking water for 13 weeks (NTP, 1993). Based on the results of this study, mice appear to be less sensitive than rats to 2-ethoxyethanol-induced toxic effects. As in rats, the male reproductive system was a target organ in mice, with effects on weight and histopathology of testes observed at 5123 mg/kg-bw per day and above and 7284 mg/kg-bw per day, respectively, while effects on sperm parameters were noted at 5123 mg/kg-bw per day or more. In addition, effects on the estrous cycle were observed in females exposed to 1304 mg/kg-bw per day and above. Although hematological parameters were not examined in mice, hematopoiesis of the spleen was noted at the highest dose in males and at 7255 mg/kg-bw per day and above in females. The incidence of a rather rare lesion, hypertrophy of the X-zone of the adrenal gland, resulting from marked lipid vacuolization, was significantly increased in female mice administered 2725 mg/kg-bw per day or more (and non-significantly increased at 1304 mg/kg-bw per day); this lesion was not observed in any of the subchronic oral studies in rats. Based on this study, the LOELs in male and female mice are considered to be 5123 and 1304 mg/kg-bw per day, with NOELs of 2003 and 722 mg/kg-bw per day, respectively.

2.4.3.4.2 Inhalation

Identified information on the subchronic toxicity of inhaled 2-ethoxyethanol and its acetate is limited to earlier studies in rats and rabbits. Exposure to 25 ppm (92 mg/m^3) 2-ethoxyethanol or more for 13 weeks was irritating to the eyes and nose of Sprague-Dawley rats. However, no exposure-related lesions were observed in the extensive range of tissues examined at the highest concentration of 400 ppm (1472 mg/m^3) (other exposure groups were not examined), and the only systemic effects noted were reductions in relative weights of the pituitary gland in males and the spleen in females exposed to 400 ppm (1472 mg/m^3) and alterations in leukocyte count and blood urea nitrogen in female rats at the highest concentration (Barbee *et al.*, 1984). In male and female Wistar rats exposed to 200 ppm 2-ethoxyethyl acetate (approximately equivalent to 737 mg 2-ethoxyethanol/m^3) for 10 months, no hematological effects were noted, and the only histopathological change observed was renal tubular nephritis in males, although only a limited range of tissues was examined (Truhaut *et al.*, 1979).

Exposure to airborne 2-ethoxyethanol (• 25 ppm [92 mg/m^3]) was also irritating to the eyes and nose of rabbits. Reduced weight and degeneration of the testes were observed at 400 ppm (1472 mg/m^3) (histopathological examinations do not appear to have been conducted in animals exposed to lower concentrations), while anemia was present in both sexes at this concentration (Barbee *et al.*, 1984). As in rats, exposure to 200 ppm 2-ethoxyethyl acetate (equivalent to 737 mg 2-ethoxyethanol/m^3) via inhalation resulted in renal tubular nephritis in males; no effects on reproductive organs or blood parameters were reported (Truhaut *et al.*, 1979).

2.4.3.5 Chronic toxicity and carcinogenicity

Although a final version of the only relevant chronic study identified was never published (data analyses were never completed due to problems encountered with the laboratory conducting the study; Eastin, 2000), according to an early account of preliminary results, the testes were the principal target in both rats and mice orally exposed to 2-ethoxyethanol for 2 years (Melnick, 1984).

2.4.3.6 Genotoxicity

The available information on the genotoxicity of 2-ethoxyethanol suggests that 2-ethoxyethanol may have some weak potential, at most, to induce cytogenetic damage, but there is no evidence that it induces mutations. Neither 2-ethoxyethanol nor its acetate was mutagenic in several *in vitro* assays in *Salmonella* (Ong, 1980; Shimizu *et al.*, 1985; Zeiger *et al.*, 1985; Guzzie *et al.*, 1986; Slesinski *et al.*, 1988; Hüls AG, 1989; Hoflack *et al.*, 1995) or in a limited number of studies in cultured mammalian cells (Guzzie *et al.*, 1986; Myhr *et al.*, 1986; Slesinski *et al.*, 1988). Mixed or equivocal results have been reported for the induction of chromosomal aberrations, micronuclei or sister chromatid exchange by 2-ethoxyethanol or 2-ethoxyethyl acetate in various mammalian cell lines (Guzzie *et al.*, 1986; Galloway *et al.*, 1987; Slesinski *et al.*, 1988; Villalobos-Pietrini *et al.*, 1989; Elias *et al.*, 1996). 2-Ethoxyethanol did not induce morphological transformation or aneuploidy *in vitro*, although it did show weak potential to interfere with mitotic division (Elias *et al*., 1996). While neither of the two principal metabolites of 2-ethoxyethanol, EALD and EAA, was mutagenic in *Salmonella* (Hoflack *et al*., 1995), the acetaldehyde consistently tested positive for numerous cytogenetic endpoints *in vitro*, although results for the acetic acid metabolite were negative or equivocal (Elias *et al*., 1996).

In the limited *in vivo* database, there was no evidence of the induction of micronuclei in the bone marrow of mice exposed to 2-ethoxyethanol, 2-ethoxyethyl acetate or EAA (Guzzie *et al*., 1986; Slesinski *et al*., 1988; Elias *et al*., 1996).

2.4.3.7 Developmental toxicity

2.4.3.7.1 Oral

Although only limited information is available on the developmental effects of 2-ethoxyethanol following oral exposure, adverse effects, including increased implantation loss, resorptions and embryo mortality, decreased fetal body weight and various skeletal and cardiovascular abnormalities, were observed in multiple strains of rats, often in the absence of maternal toxicity (Stenger *et al*., 1971; Goad and Cranmer, 1984; Chester *et al*., 1986). In only one of the three limited accounts could a NOEL be determined (NOEL = 47 mg/kg-bw per day; LOEL = 94 mg/kg-bw per day) (Stenger *et al*., 1971). Similar developmental effects were observed at doses lower than those that were maternally toxic in the only identified relevant study in mice; severe malformations (e.g., exencephaly) were observed at higher doses (Wier *et al*., 1987). Although the doses investigated in mice were lower than those in rats, mice appear to be less sensitive than rats to the developmental toxicity of ingested 2-ethoxyethanol, as only reduced fetal body weight was observed at the lowest dose tested (i.e., 1000 mg/kg-bw per day), whereas increased abnormalities were noted in rats at much lower doses.

2.4.3.7.2 Inhalation

The developmental toxicity of inhaled 2-ethoxyethanol and its acetate has been investigated in rats and rabbits. In many of these studies, fetotoxic effects were observed in multiple strains at concentrations lower than those causing maternal toxicity. In Wistar-derived Alpk/AP rats, the lowest concentration of 2-ethoxyethanol reported to induce developmental effects (skeletal variations) in the absence of maternal toxicity was 50 ppm (184 mg/m^3), with a NOEL of 10 ppm (37 mg/m^3) (Doe, 1984). In Sprague-Dawley and Fischer 344 rats, exposure to 2-ethoxyethyl acetate during gestation also resulted in increased incidences of skeletal variations at the lowest concentrations tested (130 and 50 ppm, respectively, equivalent to 479 and 184 mg 2-ethoxyethanol/m^3) (Nelson *et al*., 1984; Tyl *et al*., 1988).

Exposure to 2-ethoxyethanol during pregnancy also induced neurological effects in the developing young, based on behavioural differences, consistent with decreased neuromotor function, and alterations in levels of several neurochemicals (particularly in the cerebrum) observed in Sprague-Dawley rats exposed to 100 ppm (368 mg/m^3; the lowest concentration tested) and above (Nelson *et al*., 1981, 1982a,b).

In Dutch rabbits, Tinston (1983a) observed reduced mean number of implantations and number of live fetuses at 50 ppm (184 mg/m^3) 2-ethoxyethanol (the lowest concentration investigated) or more, in the absence of maternal effects. Conversely, Doe (1984) reported no clear effects on these endpoints at concentrations up to 175 ppm (644 mg/m^3); however, there were increased incidences of skeletal defects and variations at this exposure level, but not at lower concentrations (10 or 50 ppm [37 or 184 mg/m^3]). Developmental effects (increased malformations, anomalies and skeletal variations) were also observed in fetuses of New Zealand white rabbits exposed to 160 ppm (589 mg/m^3) 2-ethoxyethanol (the lowest concentration tested) during gestation; slight maternal toxicity was also present at this exposure level. 2-Ethoxyethyl acetate was also developmentally toxic in both these strains of rabbits, with a LOEL of 100 ppm (equivalent to 368 mg 2-ethoxyethanol/m^3), although no effects were noted at lower concentrations (25 or 50 ppm as the acetate, equivalent to 92 or 184 mg 2-ethoxyethanol/m^3) (Tinston, 1983b; Doe, 1984; Tyl *et al*., 1988).

2.4.3.7.3 Dermal

Dermally applied 2-ethoxyethanol or its acetate induced developmental effects, including increased resorptions, reduced number of live fetuses per litter, decreased fetal body weights and increased incidence of visceral malformations (predominantly of the cardiovascular system) and skeletal variants, in Sprague-Dawley rats at all doses tested (i.e., • 4000 mg/kg-bw per day, a dose that was not or only slightly maternally toxic) (Hardin *et al*., 1982, 1984).

2.4.3.8 Reproductive toxicity

2.4.3.8.1 Oral

The majority of the relevant studies identified have been conducted by the oral route in male rats or mice. Ingested 2-ethoxyethanol, as well as the acetate moiety and the acetic acid metabolite, consistently induced effects on male reproductive organs or sperm parameters in multiple strains of both species. Testicular and epididymal weights were reduced in Long-Evans, Sprague-Dawley, F344/N and CR,COBS,CD,BR rats administered doses of 200 mg/kg-bw per day or more by gavage in water or olive oil or in the drinking water for 4 weeks or longer (Krasavage and Vlaovic, 1982; Oudiz and Zenick, 1986; NTP, 1993; Chung *et al*., 1999), but not in Long-Evans rats exposed to 150 mg/kg-bw per day by gavage in water for 6 weeks (Hurtt and Zenick, 1986) or Sprague-Dawley rats administered 250 mg/kg-bw per day by gavage in water for 11 days (Foster*et al*., 1983) (although these effects were noted at greater doses in rats exposed for these durations). Histopathological effects on the testes and spermatocytes were noted following oral exposure to 450 mg/kg-bw per day (the lowest dose tested) or more for 6 weeks (Krasavage and Vlaovic, 1982). Reductions in testicular or epididymal sperm counts or alterations in sperm motility or morphology were noted at doses as low as 150 mg/kg-bw per day (the lowest dose tested) when administered for 6 weeks or longer, with regularly mated males being more sensitive to these effects than non-mated rats (Hurtt and Zenick, 1986). Sperm counts were not assessed in the only study in which lower doses were investigated (i.e., Chung *et al.*, 1999) or in a shorter-term study (11 days) in rats administered 250 mg/kg-bw per day (Foster *et al.*, 1983), although spermatocyte degeneration was observed in the latter study only at 500 mg/kg-bw per day or more. Repeated oral administration of EAA, the predominant metabolite of 2-ethoxyethanol, induced a similar profile of male reproductive effects in rats (Foster *et al.*, 1983, 1987), suggesting that this metabolite may be, at least in part, responsible for these effects.

Reduction in testicular or epididymal weights or alterations in sperm parameters were also observed in mice orally exposed to 2-ethoxyethanol or 2-ethoxyethyl acetate for 5 weeks or longer (Nagano *et al.*, 1979, 1984; Morrissey *et al.*, 1989; NTP, 1993; Chapin and Sloane, 1997), although this species appears to be less sensitive than rats, as the lowest dose associated with male reproductive effects in mice was 1000 mg/kg-bw per day (with a NOEL of 500 mg/kg-bw per day).

Although not as extensively investigated as in males, exposure to 2-ethoxyethanol in the drinking water for 13 weeks induced effects on the estrous cycle in female rats and mice at doses of 804 and 1304 mg/kg-bw per day or more, respectively, with uterine atrophy occurring in rats at higher doses (NTP, 1993).

Two oral studies were identified in which the effects of exposure to 2-ethoxyethanol, 2-ethoxyethyl acetate or EAA on reproductive ability were assessed in mice. In a continuous breeding study, in which both sexes were exposed in the drinking water, all three substances adversely affected reproductive success (in terms of decreased fertility and reductions in numbers and weights of pups), with the LOEL for 2-ethoxyethanol being approximately 1650 mg/kg-bw per day, while no adverse effects were noted at 850 mg/kg-bw per day. Effects were observed at all doses of the EAA metabolite tested (i.e., • 300 mg/kg-bw per day). The results of cross-over mating trials indicated that exposure of either sex to 2-ethoxyethanol or its acetate adversely affected reproductive ability, while such effects were noted when only females were exposed to 2-ethoxyacetic acid. However, effects on reproductive organs and sperm or estrous cycle parameters were observed at similar doses for all compounds. Continuous exposure *in utero* and until mating to 1860 mg/kg-bw per day of 2-ethoxyethyl acetate also induced effects on reproductive success and organs and sperm parameters in males of the second generation; however, the authors indicated that it was unclear if the second generation was more sensitive than the first (Morrissey *et al.*, 1989; Chapin and Sloane, 1997). In a secondary account of a similar continuous-breeding study in mice (Gulati *et al.*, 1985), similar effects on reproductive success were observed at doses of 1800 mg/kg-bw per day or more of 2-ethoxyethyl acetate (which were attributed to exposure of females in a cross-over study) as well as effects on sperm and testes in males; in addition, histopathological changes in the testes were observed in the second generation.

2.4.3.8.2 Inhalation

In subchronic studies in experimental animals, reduced testes weight and degeneration of the seminiferous tubules were noted in rabbits exposed to 400 ppm (1472 mg/m^3); however, effects on the testes were not observed in similarly exposed rats (Barbee *et al.*, 1984) or in rats or rabbits exposed to higher concentrations of the acetate (Truhaut *et al.*, 1979).

In the only inhalation study on the effects of 2-ethoxyethanol on reproductive ability identified, no effects on mating behaviour or fertility were observed in female rats exposed to up to 649 ppm (2388 mg/m^3) for 3 weeks prior to mating with unexposed males (Andrew and Hardin, 1984).

2.4.3.9 Immunological effects

In the two relevant studies identified, there was no evidence that exposure to 2-ethoxyethanol or its acetate induced adverse effects on the immune system in rats or mice (the highest dose tested was 2400 mg/kg-bw per day for 10 days) (Houchens *et al.*, 1984; Smialowicz *et al.*, 1992).

2.4.4 Humans

Several epidemiological studies, designed to investigate the potential effects on the lymphohematopoietic system or on reproduction and development, have been conducted in populations exposed to 2-ethoxyethanol or its acetate in the occupational environment. However, in most of these studies, many of which involved small populations, workers were also exposed to various other substances in the workplace. Although these studies are limited, effects on the blood and, possibly, reproductive effects in men were observed.

In a recent well-conducted cross-sectional study (Kim *et al.*, 1999), effects on white blood cells, suggestive of bone marrow depression, were observed in a group of 57 painters exposed to 2-ethoxyethyl acetate. White blood cell and granulocyte counts were reduced in an exposure-related manner in both the high- and low-exposure groups of workers (statistically significantly lower in those exposed to mean concentrations of 3.03 ppm 2-ethoxyethyl acetate [approximately equivalent to 11 mg 2-ethoxyethanol/m^3], although not considered by the authors to be clinically significantly decreased), while a significantly higher proportion of all exposed painters had leukopenia. These effects remained after controlling for several potentially confounding factors. Bone marrow hypoplasia was noted in the three leukopenic men examined. The authors also noted that mean corpuscular volume was increased in the high-exposure group, which the authors hypothesized may be an early indicator of anemia. An increase in the prevalence of anemia was observed in a group of 94 shipyard painters exposed to similar mean concentrations of 2-ethoxyethanol (2.7 ppm [10 mg/m^3]), along with several other substances (Welch and Cullen, 1988). Hemoglobin levels had declined since first employment in these workers, but were not related to duration of exposure. Exposed workers also had a slightly higher prevalence of low polymorphonuclear leukocyte counts. Bone marrow hypoplasia was also observed in a survey of seven printers exposed to 2-ethoxyethanol and other substances (Cullen *et al.*, 1983).

Although only three relevant epidemiological investigations have been identified, reduced sperm production was consistently observed in populations occupationally exposed to mean concentrations of 2-ethoxyethanol of 9.9 or 24 mg/m^3 (with maximum levels up to 88 mg/m^3), along with other substances (Welch *et al.*, 1988; Ratcliffe *et al.*, 1989; Schrader *et al.*, 1996). In a case–control study of 1019 men with a clinical diagnosis of infertility or reduced fertility, there was a significant association between this diagnosis and the detection of EAA in the urine (odds ratio = 3.11) (Veulemans *et al.*, 1993). There was no consistent evidence of effects on male or female reproductive ability in other investigations of men or women exposed to 2-ethoxyethanol, although most of these studies are limited by the mixed exposures of the study populations and the lack of analyses for associations with 2-ethoxyethanol specifically (Beaumont *et al.*, 1995; Schenker *et al.*, 1995; Swan *et al.*, 1995; Correa *et al.*, 1996; Gray *et al.*, 1996; Ha *et al.*, 1996; Schenker, 1996; Swan and Forest, 1996; Chia *et al.*, 1997).

3.0 PROPOSED ASSESSMENT OF "TOXIC" UNDER CEPA 1999

3.1 CEPA 1999 64(a): Environment

The environmental risk assessment of a PSL substance is based on the procedures outlined in Environment Canada (1997a). Analysis of exposure pathways and subsequent identification of sensitive receptors are used to select environmental assessment endpoints (e.g., adverse reproductive effects on sensitive fish species in a community). For each endpoint, a conservative Estimated Exposure Value (EEV) is selected and an Estimated No-Effects Value (ENEV) is determined by dividing a Critical Toxicity Value (CTV) by an application factor. A conservative (or hyperconservative) quotient (EEV/ENEV) is calculated for each of the assessment endpoints in order to determine whether there is potential ecological risk in Canada. If these quotients are less than one, it can be concluded that the substance poses no significant risk to the environment, and the risk assessment is completed. If, however, the quotient is greater than one for a particular assessment endpoint, then the risk assessment for that endpoint proceeds to an analysis where more realistic assumptions are used and the probability and magnitude of effects are considered. This latter approach involves a more thorough consideration of sources of variability and uncertainty in the risk analysis.

3.1.1 Assessment endpoints

In Canada, most environmental releases of 2-ethoxyethanol are to the atmosphere. Based on its predicted environmental partitioning, assessment endpoints for 2-ethoxyethanol relate to terrestrial organisms, including terrestrial wildlife and soil organisms, and aquatic organisms.

3.1.2 Environmental risk assessment

3.1.2.1 Terrestrial organisms

3.1.2.1.1 Wildlife

For a conservative risk characterization for terrestrial biota, the EEV is 860 ng/m^3, the highest concentration of 2-ethoxyethanol reported in Canada (near an automotive plant in Windsor) (OMEE, 1994).

The CTV is 50 ppm (1.8×10^8 ng/m^3), the concentration that had minimal fetotoxic effects on rats and rabbits in inhalation studies. Dividing this CTV by a factor of 100 (to account for the extrapolation from laboratory to field conditions and interspecies and intraspecies variations in sensitivity) gives an ENEV of 0.5 ppm (1.8×10^6 ng/m^3).

The conservative quotient is calculated as follows:

$$\text{Quotient} = \frac{\text{EEV}}{\text{ENEV}}$$

$$= \frac{860 \text{ ng/m}^3}{1.8 \times 10^6 \text{ ng/m}^3}$$

$$= 4.78 \times 10^{-4}$$

Therefore, concentrations of 2-ethoxyethanol in air in Canada are unlikely to cause adverse effects on populations of wildlife.

3.1.2.1.2 Soil organisms

For a conservative risk characterization for soil organisms, the EEV is 4.15×10^{-4} ng/g, the estimated concentration of 2-ethoxyethanol in soil using ChemCAN modelling based on reported releases in 1995. This value is believed to be conservative because releases of 2-ethoxyethanol in Canada appear to have significantly decreased since 1995.

No information was identified regarding the toxicity of 2-ethoxyethanol to soil organisms. Van Leeuwen *et al*. (1992) used quantitative structure–activity relationships to estimate that a sediment concentration of 2800 ng 2-ethoxyethanol/g would be hazardous to 5% of benthic species (HC_5). Using this sediment HC_5 value as a CTV and an application factor of 100 (to account for the extrapolation from benthic to soil organisms) gives an ENEV of 28 ng/g for soil organisms.

The conservative quotient is calculated as follows:

$$\text{Quotient} = \frac{\text{EEV}}{\text{ENEV}}$$

$$= \frac{4.15 \times 10^{-4} \text{ ng/g}}{28 \text{ ng/g}}$$

$$= 1.48 \times 10^{-5}$$

Therefore, concentrations of 2-ethoxyethanol in soil in Canada are unlikely to cause adverse effects on populations of soil organisms.

3.1.2.2 Aquatic organisms

For a conservative risk characterization for aquatic organisms, the EEV is 2.2×10^{-5} µg/L, the estimated concentration of 2-ethoxyethanol in water using ChemCAN modelling based on reported releases in 1995. This value is believed to be conservative because releases of 2-ethoxyethanol in Canada appear to have significantly decreased since 1995.

The CTV for aquatic organisms is 7.7×10^{6} µg/L, the 48-hour IC_{50} for *Daphnia magna*. Dividing this CTV by a factor of 100 (to account for the conversion of a short-term IC_{50} to a long-term no-effects value, extrapolation from laboratory to field conditions, and interspecies and intraspecies variations in sensitivity) gives an ENEV of 7.7×10^{4} µg/L.

The conservative quotient is calculated as follows:

$$\text{Quotient} = \frac{\text{EEV}}{\text{ENEV}}$$

$$= \frac{2.2 \times 10^{-5}\ \mu g/L}{7.7 \times 10^{4}\ \mu g/L}$$

$$= 2.9 \times 10^{-10}$$

Therefore, concentrations of 2-ethoxyethanol in water in Canada are unlikely to cause adverse effects on populations of aquatic organisms.

3.1.2.3 Discussion of uncertainty

There are several sources of uncertainty in this environmental risk assessment. Few data on environmental concentrations of 2-ethoxyethanol in Canada or elsewhere were identified; limited monitoring data were identified for air only. The EEV for wildlife exposure is considered to be conservative, as it was based on the maximum concentration measured near an industrial facility in Windsor. In addition, 2-ethoxyethanol was not detected in ambient air in the multimedia exposure study in Canada (Conor Pacific Environmental Technologies, 1998) or in a survey of six locations in the United States (Sheldon *et al.*, 1988).

In view of the lack of adequate monitoring data, the ChemCAN4 model was used to estimate concentrations of 2-ethoxyethanol in the other environmental compartments (i.e., soil and water), based on the highest reported recent release of the substance in Canada, which occurred in 1995. Kane (1993) compared measured environmental concentrations of five industrial chemicals and six pesticides with environmental concentrations estimated for the substances by the ChemCAN model. Sixty percent of the measured environmental concentrations were within 1 order of magnitude of predicted values, and 75% were within 2 orders of magnitude. In the only relevant study identified from other countries, the concentration of 2-ethoxyethanol in a polluted river in Japan ranged up to 1200 μg/L (Yasuhara *et al.*, 1981), a value that is an order of magnitude lower than the ENEV for aquatic organisms.

No information was identified regarding the toxicity of 2-ethoxyethanol to soil organisms or to terrestrial wildlife through atmospheric exposure. An estimation of a hazardous concentration to benthic species was the basis for the assessment of risk to soil organisms. The results of an inhalation toxicity study using a laboratory strain of rats were used for the assessment of risk to terrestrial biota. To account for these uncertainties, application factors were used in the environmental risk assessment to derive ENEVs.

Conservative risk quotients were very small for all environmental assessment endpoints. Therefore, despite the data gaps regarding the environmental concentrations and the effects of 2-ethoxyethanol on soil organisms and terrestrial wildlife, the data available at this time are considered adequate for drawing a conclusion about the environmental risk of the substance in Canada.

3.2 CEPA 1999 64(b): Environment upon which life depends

2-Ethoxyethanol does not deplete stratospheric ozone, and its potential for contributing to climate change is negligible. The potential of 2-ethoxyethanol for creation of photochemical ozone (smog) is moderate, but the low quantities of 2-ethoxyethanol in the atmosphere are unlikely to make its contribution significant relative to that of other smog-forming substances.

3.3 CEPA 1999 64(c): Human health

3.3.1 Estimates of potential exposure in humans

The limitations of the available monitoring data for 2-ethoxyethanol preclude the development of reliable estimates of typical exposure of the general population; instead, crude upper-bounding estimates of exposure to 2-ethoxyethanol from environmental media and consumer products have been developed in order to characterize potential exposure from these pathways.

The only environmental media for which available monitoring data allowed even crude estimation of exposure were air and water. Upper-bounding estimates of intake of 2-ethoxyethanol from these media by six age groups in the general population of Canada are presented in Table 2. These estimates are based on the limits of detection in air and tap water from the limited Canadian multimedia exposure study in which concentrations of 2-ethoxyethanol were below the limits of detection in all samples analysed (Conor Pacific Environmental Technologies, 1998). Although confidence in the results of this survey is low, comparison with estimates of intake in air and water on the basis of results of fugacity modelling and in ambient air based on the data from the Windsor study indicates that this approach is conservative in deriving upper-bounding estimates of intake in air. Based on these values, the average adult in Canada would be exposed to airborne levels of 2-ethoxyethanol no greater than 3.6 μg/m^3 and would not ingest more than 0.005 μg/kg-bw per day in drinking water, although it is recognized that these values likely overestimate exposure.

Since no monitoring data are available, it is not possible to determine the contribution of food to the overall intake of 2-ethoxyethanol. However, 2-ethoxyethanol is released primarily to air from industrial activities and through volatilization from consumer products and is unlikely to partition to food from air due to its volatility and very low octanol/water partition coefficient (log K_{ow} of –0.32). In addition, if intake in food is estimated on the basis of extrapolation from the results of fugacity modelling, this value would be several orders of magnitude less than the upper-bounding estimates calculated for air and drinking water on the basis of the limits of detection in the multimedia study. Likewise, exposure to 2-ethoxyethanol in soil is likely to be negligible in comparison with that in air, based on its release patterns and the relatively small quantities ingested.

Direct exposure to 2-ethoxyethanol and 2-ethoxyethyl acetate can result from the use of a variety of consumer products containing these substances. Both inhalation and dermal absorption are expected to be important routes of exposure for most consumer products, since many of those expected to contain 2-ethoxyethanol or its acetate can contact the skin. Because most of the consumer products for which suitable data are available are used primarily by adults, the estimated exposures have been derived for this age class only. (The differences among age classes in intake from a given medium as a result of age-specific differences would be small in relation to the variation in exposure from the various sources, in any case.) Upper-bounding estimates of intake of 2-ethoxyethanol (on a per event basis as well as average daily intakes based on annual event frequencies) from exposure to household cleaning products and floor wax/polish were developed from product use scenarios (Versar Inc., 1986), assuming 100% absorption for the product contacting the skin and for the inhaled product and 100% transfer of 2-ethoxyethanol from the product into air (in view of the lack of adequate data to support more refined estimates) (Table 3). These estimates should be interpreted with caution in view of the limited available information on the presence and concentrations of 2-ethoxyethanol and its acetate in consumer products currently used in Canada and should be considered as upper-bounding estimates only, as actual exposure is very likely much lower. Indeed, as discussed above, 2-ethoxyethanol was not detected in a recent investigation conducted by Health Canada of emissions of glycol ethers from several consumer products (Cao, 1999).

The highest estimated worst-case intake on a per event basis from products containing 2-ethoxyethanol was for floor wax/polish (i.e., 12 mg/kg-bw via inhalation and an additional 0.6 mg/kg-bw via dermal absorption when applied by rag), although intakes are much lower when averaged on a daily basis, taking into consideration the low frequency of use. Concentrations in indoor air resulting from use of such products could range up to 1075 mg/m^3, assuming complete volatilization. For products that may be used on an almost daily basis, the highest estimated upper-bounding intake was for all-purpose spray cleaner (1.6 mg/kg-bw per day by inhalation and 0.5 mg/kg-bw per day by dermal exposure); the worst-case estimate of concentrations of 2-ethoxyethanol in indoor air resulting from use of this product is 190 mg/m^3.

Upper-bounding estimates of intake of 2-ethoxyethyl acetate from exposure to products containing the acetate moiety (data were limited to paints and paint thinners) were also developed from product use scenarios (Versar Inc., 1986), assuming 100% absorption for the product contacting the skin and for the inhaled product and 100% volatilization (Table 3). These worst-case estimates of intake were higher than those developed for 2-ethoxyethanol (up to 1545 mg/kg-bw per event for inhalation intake from latex or oil-based paints, equivalent to 1053 mg 2-ethoxyethanol/kg-bw, with average daily intakes being lower due to the infrequent use). The highest indoor air concentrations of 2-ethoxyethyl acetate are estimated to result from use of paint thinner, with upper-bounding values of 26 064 mg 2-ethoxyethyl acetate/m^3 (equivalent to 17 776 mg 2-ethoxyethanol/m^3), assuming 100% transfer to air.

It should be noted that these estimates have been made for only a limited range of media and products for which at least some data were available. In addition, they do not represent typical exposures, since the limitations of the available data preclude development of such estimates; most are instead upper-bounding estimates of potential exposure.

3.3.2 Human health hazard characterization

Little information was identified on the effects of 2-ethoxyethanol in humans. However, although the epidemiological data are not conclusive, the results of available investigations in occupationally exposed populations are suggestive of effects on the blood and on sperm production in men (Cullen *et al*., 1983; Welch and Cullen, 1988; Welch *et al*., 1988; Ratcliffe *et al*., 1989; Veulemans *et al*., 1993; Kim *et al*., 1999). There is consistent evidence from short- and long-term toxicological studies in all species of experimental animals investigated that hematological, male reproductive and developmental effects are associated with exposure to 2-ethoxyethanol or its acetate by the oral, inhalation and dermal routes. The results of mechanistic studies suggest that metabolic activation to the acetic acid metabolite, EAA, is required for the induction of these effects. For example, co-exposure to substances that interfere with metabolism via alcohol or aldehyde dehydrogenases (e.g., toluene, xylene and ethanol) reduced the magnitude of testicular atrophy in male rats (Chung *et al*., 1999) and the effects on neurological development in rats exposed to 2-ethoxyethanol *in vitro* (Nelson *et al*., 1982a,b, 1984). Metabolism via alcohol and aldehyde dehydrogenases to EAA is the principal metabolic pathway in both humans and laboratory animals; indeed, there is some evidence, although limited, that humans may have greater potential than rats for formation of EAA and slower clearance than in rats. Therefore, although there is only limited evidence of effects on the blood and sperm production in occupationally exposed human populations, based on the consistent evidence in experimental animals and the similarity in metabolism across species, hematopoietic, reproductive (in males) and developmental toxicity are considered critical effects for 2-ethoxyethanol.

3.3.3 *Human health risk characterization*

As discussed above in Section 1.0, due principally to the limitations of available monitoring data, estimates of upper-bounding estimates of exposure are compared with conservative effect levels for critical effects as a basis for characterization of rather crude margins of exposure.

Based on evaluation of available data, hematological, reproductive and developmental effects are considered critical endpoints for assessment of potential risk to humans associated with exposure to 2-ethoxyethanol. Statistically significant alterations in blood parameters were observed in shipyard painters exposed to a mean 2-ethoxyethyl acetate concentration of 3.03 ppm (equivalent to 11 mg 2-ethoxyethanol/m^3),[5] although the authors suggested that the magnitude of these changes was not of biological significance (Kim *et al*., 1999). With respect to reproductive effects, in the only relevant studies in which exposure was quantified, reduced sperm production was observed in workers exposed to mean 2-ethoxyethanol concentrations of 9.9 mg/m^3 (Welch *et al*., 1988) and 24 mg/m^3 (Ratcliffe *et al*., 1989), although these men were also exposed to several other substances. In investigations in experimental animals, effect levels for hematological, reproductive and developmental effects were generally greater than concentrations associated with effects in the epidemiological studies (i.e., lowest LOELs of 184 mg/m^3 and 94 mg/kg-bw per day), which is consistent with the limited data that suggest that humans form the putatively active metabolite to a greater extent than do rats and clear the metabolite more slowly. Therefore, risk to human health is characterized through comparison of the upper-bounding estimates of population exposure with the levels associated with effects in exposed workers.

Based on comparison of the concentration associated with effects in humans in the study in which exposure was best characterized (i.e., alterations in hematological parameters in Kim *et al*., 1999) of 11 mg/m^3 with the upper-bounding estimates of exposure levels in air in Canada of 3.6 μg/m^3 (based on the detection limit in the multimedia exposure study by Conor Pacific Environmental Technologies, 1998), the margin between effect level and exposure is about 3000. (Note: If this effect level is compared with the highest concentration of 2-ethoxyethanol detected outside of an automotive plant in Windsor [i.e., the maximum level detected in ambient air in Canada, 0.86 μg/m^3], this margin would be even greater.) With respect to ingestion, although no epidemiological investigations of the effects of ingested 2-ethoxyethanol in humans were identified, the margin between the intake equivalent to inhalation of 2-ethoxyethanol at a concentration of 11 mg/m^3 (assuming 100% absorption) and the upper-bounding estimate of intake in drinking water is about 6 orders of magnitude. Margins between exposure and the effect levels from studies in animals would be even greater. Although intake of 2-ethoxyethanol in food could not be estimated, it is considered unlikely to be greater than these upper-bounding estimates for air or drinking water. These margins between upper-bounding estimates of exposure and the conservative effect levels are considered adequate to account for the uncertainties in the database (including exposure estimates and interindividual variation in response).

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[5] Since the acetate moiety of 2-ethoxyethanol is rapidly converted to 2-ethoxyethanol in the body, with similar resulting health effects, it was considered appropriate to develop effect levels on the basis of studies in which the toxicity of 2-ethoxyethyl acetate was investigated, converting the exposure levels of the acetate to equivalent concentrations or doses of 2-ethoxyethanol on a relative molecular weight basis.

However, upper-bounding estimates of exposure to 2-ethoxyethanol through use of some consumer products could approach or exceed the effect levels for health effects in humans. For example, upper-bounding estimates of indoor air concentrations resulting from use of paint thinners containing the substance (the highest estimated exposure level from consumer products) are 3 orders of magnitude greater than these effect levels. However, the degree of confidence in these estimates of exposure from consumer products is considered to be extremely low (see Section 3.3.4), and they are very likely gross overestimates of actual exposure from products currently being used in Canada. Therefore, research into the use of consumer products containing 2-ethoxyethanol in Canada and concentrations of 2-ethoxyethanol in these products is considered to be a high priority.

3.3.4 Uncertainties and degree of confidence in the human health risk characterization

Due to the paucity of data on levels of 2-ethoxyethanol in environmental media in Canada, there is a high degree of uncertainty in the estimates of exposure that have been developed in this assessment. While conservative upper-bounding estimates of exposure were determined on the basis of the detection limits reported in the multimedia exposure study, it is not known if these values grossly overestimate environmental levels or if the population is exposed to concentrations approaching these levels, although predicted concentrations in ambient air and drinking water based on fugacity modelling were several orders of magnitude below these detection limits, and levels were lower in the small survey of ambient air in Windsor (in which confidence is greater) than the detection limit reported for the multimedia study. In addition, although these data are considered adequate as a basis for developing crude bounding estimates of exposure, the methodology employed in the multimedia study is considered experimental, for which confidence is low. Recoveries were often low (only 43% for 2-ethoxyethanol in air), concentrations in "blanks" were high, etc. There is a high degree of confidence, though, that this approach is conservative, based on comparison with other results. It should also be noted that uptake of 2-ethoxyethanol vapour via dermal absorption has not been considered in these estimates of exposure. As well, the contribution of food and soil to overall intake of 2-ethoxyethanol is unknown, as no relevant data were identified, although predictions based on fugacity modelling suggest that intake from these sources is likely much less than the upper-bounding estimates of intake from air and drinking water upon which the conclusions presented here are based.

There is an extremely low degree of confidence in the estimates of exposure to 2-ethoxyethanol from consumer products, due to the uncertainties regarding the presence and concentrations of the substance in products currently used in Canada. Therefore, it is likely that the values presented here greatly overestimate potential current exposures. These estimates were also determined based on the conservative assumptions of complete transfer of 2-ethoxyethanol from the product to air and 100% absorption of the inhaled substance and the amount contacting the skin. While 2-ethoxyethanol was not detected in emissions from a range of products recently tested by Health Canada (Cao, 1999), acquisition of additional data on its presence in consumer products is desirable.

There is a moderate to high degree of confidence in the characterization of the health hazards associated with exposure to 2-ethoxyethanol for the purposes of identifying critical effects for risk characterization. Hematological, reproductive and developmental effects were consistently observed in investigations in experimental animals. Hematological and reproductive effects have also been observed in occupationally exposed human populations, although the database in humans is somewhat limited. Additional investigations of exposed workers, in which exposure to 2-ethoxyethanol is quantified, would be helpful in further characterizing risks to humans, particularly since there is some indication that humans may be more sensitive than animal species to effects induced by this substance (additional research on the relative toxicokinetics would also be desirable). However, there is some uncertainty concerning the effects of 2-ethoxyethanol following long-term exposure, as no adequate chronic studies in animals are available. Likewise, no epidemiological investigations of the potential effects in humans in which both magnitude and duration of exposure to 2-ethoxyethanol were considered have been identified.

3.4 Proposed conclusions

CEPA 1999 64(a): Based on conservative estimates of exposure and effects in Canada, risk quotients for terrestrial wildlife, soil organisms and aquatic organisms are less than one. The environmental risks associated with estimated concentrations of 2-ethoxyethanol likely to be found in Canada therefore appear to be low. Therefore, available data indicate that it is unlikely that 2-ethoxyethanol is entering or may enter the environment in a quantity or concentration or under conditions that have or may have an immediate or long-term harmful effect on the environment or its biological diversity, and it is proposed that it should not be considered "toxic" as defined in CEPA 1999 Paragraph 64(a).

CEPA 1999 64(b): 2-Ethoxyethanol is not involved in the depletion of stratospheric ozone and likely does not contribute significantly to climate change. Because of its very low estimated concentration in air in Canada, it is unlikely to play a significant role in tropospheric ozone production. Therefore, based on available data, it has been concluded that 2-ethoxyethanol is not entering the environment in a quantity or concentration or under conditions that constitute or may constitute a danger to the environment on which life depends, and it is proposed that it should not be considered "toxic" as defined in CEPA 1999 Paragraph 64(b).

CEPA 1999 64(c): Based on consideration of the margins between upper-bounding estimates of population exposure to 2-ethoxyethanol in the general environment in Canada and conservative effect levels, 2-ethoxyethanol is not considered to be "toxic" as defined in CEPA 1999 Paragraph 64(c). However, although on the basis of very limited information, upper-bounding estimates of exposure to 2-ethoxyethanol through use of some consumer products could approach or exceed conservative effect levels. Although 2-ethoxyethanol was not detected in emissions from a range of consumer products tested recently in Canada, acquisition of additional data on its presence in consumer products is desirable

Proposed overall conclusion: Based on critical assessment of relevant information, it is proposed that 2-ethoxyethanol should not be considered "toxic" as defined in Section 64 of CEPA 1999.

3.5 Considerations for follow-up (further action)

Although 2-ethoxyethanol was not detected in emissions from a range of products tested by Health Canada, information on its use in consumer products marketed in Canada is sparse. It is recommended, therefore, that additional information on patterns of use of consumer products containing 2-ethoxyethanol in Canada and levels of the compound in these products be sought. Depending upon the results of such investigations, it may be necessary to conduct a fuller assessment, including refined estimates of exposure and full dose–response analysis.

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APPENDIX A: Search strategies employed for identification of relevant data

Environmental assessment

Data relevant to the assessment of whether 2-ethoxyethanol is "toxic" to the environment under CEPA were identified from existing review documents, published reference texts and on-line searches, conducted between January and May 1996, of the following databases: ASFA (Aquatic Sciences and Fisheries Abstracts, Cambridge Scientific Abstracts; 1990–1996), BIOSIS (Biosciences Information Services; 1990–1996), CAB (Commonwealth Agriculture Bureaux; 1990–1996), CESARS (Chemical Evaluation Search and Retrieval System, Ontario Ministry of the Environment and Michigan Department of Natural Resources; 1996), CHRIS (Chemical Hazard Release Information System; 1964–1985), Current Contents (Institute for Scientific Information; 1993, 1994, 1995, up to January 15, 1996), ELIAS (Environmental Library Integrated Automated System, Environment Canada library; January 1996), Enviroline (R.R. Bowker Publishing Co.; November 1995 – June 1996), Environmental Abstracts (1975 – February 1996), Environmental Bibliography (Environmental Studies Institute, International Academy at Santa Barbara; 1990–1996), GEOREF (Geo Reference Information System, American Geological Institute; 1990–1996), HSDB (Hazardous Substances Data Bank, U.S. National Library of Medicine; 1996), Life Sciences (Cambridge Scientific Abstracts; 1990–1996), NTIS (National Technical Information Service, U.S. Department of Commerce; 1990–1996), Pollution Abstracts (Cambridge Scientific Abstracts, U.S. National Library of Medicine; 1990–1996), POLTOX (Cambridge Scientific Abstracts, U.S. National Library of Medicine; 1990–1995), RTECS (Registry of Toxic Effects of Chemical Substances, U.S. National Institute for Occupational Safety and Health; 1996), Toxline (U.S. National Library of Medicine; 1990–1996), TRI93 (Toxic Chemical Release Inventory, U.S. Environmental Protection Agency, Office of Toxic Substances; 1993), USEPA-ASTER (Assessment Tools for the Evaluation of Risk, U.S. Environmental Protection Agency; up to December 21, 1994), WASTEINFO (Waste Management Information Bureau of the American Energy Agency; 1973 – September 1995) and Water Resources Abstracts (U.S. Geological Survey, U.S. Department of the Interior; 1990–1996). Reveal Alert was used to maintain an ongoing record of the current scientific literature pertaining to the potential environmental effects of 2-ethoxyethanol. Data obtained after September 30, 1999, were not considered in this assessment.

In addition, a survey of Canadian industry was carried out under the authority of Section 16 of CEPA (Environment Canada, 1997b,c). Targeted companies with commercial activities involving more than 1000 kg of 2-ethoxyethanol were required to supply information on uses, releases, environmental concentrations, effects or other data that were available to them for 2-ethoxyethanol.

Health assessment

In addition to studies included in the review prepared by BIBRA Toxicology International, recent data have been identified through searching the following databases beginning in August of 1996 using the chemical name or the CAS number for both 2-ethoxyethanol and 2-ethoxyethyl acetate: Canadian Research Index, DIALOG (Cancerlit, Environmental Bibliography, Waternet, Water Resources Abstracts, Enviroline, CAB Abstracts, Food Science and Technology Abstracts, Pollution Abstracts and NTIS), Medline, Toxline Plus and TOXNET (CCRIS [Chemical Carcinogenesis Research Information System, U.S. National Cancer Institute], GENE-TOX [Genetic Toxicology, U.S. Environmental Protection Agency] and EMIC [Environmental Mutagen Information Center database, Oak Ridge National Laboratory]). Data acquired as of January 2000 were considered for inclusion in this draft.

As well as these databases, officials at the Product Safety Bureau and Drugs Directorate of Health Canada, along with the Pest Management Regulatory Agency, were contacted to obtain information relevant to this assessment.

Table 1: Emissions of 2-ethoxyethanol and its acetate from consumer products

Product category	Number of products with detectable emissions[1]	Amount emitted (µg/g product)	Source
Cleaning compounds	4 (as 2-ethoxyethanol)	na[2]	Clinical Toxicology of Commercial Products database (CARB, 1991)
Spot/stain remover	1 (as 2-ethoxyethanol)	na	Clinical Toxicology of Commercial Products database (CARB, 1991)
Window/glass cleaner	2 (as 2-ethoxyethanol)	na	Clinical Toxicology of Commercial Products database (CARB, 1991)
Rug/upholstery cleaner	3 (as 2-ethoxyethanol)	na	Clinical Toxicology of Commercial Products database (CARB, 1991)
Coatings/inks	10 (as 2-ethoxyethanol) 4 (as 2-ethoxyethyl acetate)	na	Clinical Toxicology of Commercial Products database (CARB, 1991)
Coating thinners/strippers	6 (as 2-ethoxyethanol) 1 (as 2-ethoxyethyl acetate)	na	Clinical Toxicology of Commercial Products database (CARB, 1991)
Herbicide and fungicide	1 (as 2-ethoxyethanol)	na	Clinical Toxicology of Commercial Products database (CARB, 1991)
Medical/personal hygiene	1 (as 2-ethoxyethanol)	na	Clinical Toxicology of Commercial Products database (CARB, 1991)
Adhesives	3 (as 2-ethoxyethanol) 5 (as 2-ethoxyethyl acetate)	0.1–200 0.1–900	NASA/McDonnell Douglas Materials Testing Data Base (CARB, 1991)
Coatings	14 (as 2-ethoxyethanol) 66 (as 2-ethoxyethyl acetate)	0.09–450 0.05–1578	NASA/McDonnell Douglas Materials Testing Data Base (CARB, 1991)
Fabric	1 (as 2-ethoxyethanol) 3 (as 2-ethoxyethyl acetate)	0.23 0.07–0.7	NASA/McDonnell Douglas Materials Testing Data Base (CARB, 1991)
Pens/inks	6 (as 2-ethoxyethanol) 5 (as 2-ethoxyethyl acetate)	0.1–2800 0.49–4.3	NASA/McDonnell Douglas Materials Testing Data Base (CARB, 1991)
Foam/plastic products	2 (as 2-ethoxyethyl acetate)	0.095–0.7	NASA/McDonnell Douglas Materials Testing Data Base (CARB, 1991)

[1] No information on the number of products tested was provided in the secondary account of these studies (CARB, 1991).

[2] na = not available.

Table 2: Upper-bounding estimates of intake of 2-ethoxyethanol by various age groups in the general population

Route of exposure	**Upper-bounding estimates of intake of 2-ethoxyethanol by various age groups in the general population (µg/kg-bw per day)**					
	0–6 months[1]	**7 months–4 years[2]**	**5–11 years[3]**	**12–19 years[4]**	**20–59 years[5]**	**60+ years[6]**
Ambient air[7]	0.13	0.27	0.21	0.12	0.10	0.09
Indoor air[8]	0.87	1.87	1.46	0.83	0.71	0.62
Drinking water[9]	0.005[10]	0.002	0.002	0.001	0.001	0.001
Total	**1.0**	**2.1**	**1.7**	**0.9**	**0.8**	**0.7**

[1] Assumed to weigh 7.5 kg, to drink 0.8 L of water per day and to breathe 2.1 m^3 of air per day (EHD, 1998).

[2] Assumed to weigh 15.5 kg, to drink 0.7 L of water per day and to breathe 9.3 m^3 of air per day (EHD, 1998).

[3] Assumed to weigh 31.0 kg, to drink 1.1 L of water per day and to breathe 14.5 m^3 of air per day (EHD, 1998).

[4] Assumed to weigh 59.4 kg, to drink 1.2 L of water per day and to breathe 15.8 m^3 of air per day (EHD, 1998).

[5] Assumed to weigh 70.9 kg, to drink 1.5 L of water per day and to breathe 16.2 m^3 of air per day (EHD, 1998).

[6] Assumed to weigh 72.0 kg, to drink 1.6 L of water per day and to breathe 14.3 m^3 of air per day (EHD, 1998).

[7] Based on the limit of detection for 2-ethoxyethanol in 50 ambient air samples collected outside of Canadian residences, 3.6 µg/m^3 (Conor Pacific Environmental Technologies, 1998). The average Canadian is assumed to spend 3 hours of every day outdoors (EHD, 1998).

[8] Based on the detection limit (3.6 µg/m^3) for 2-ethoxyethanol in 50 indoor air samples collected in Canadian residences (Conor Pacific Environmental Technologies, 1998). The average Canadian is assumed to spend 21 hours of every day indoors (EHD, 1998).

[9] Based on the detection limit (0.05 µg/L) for 2-ethoxyethanol in 50 drinking water samples collected in Canadian residences (Conor Pacific Environmental Technologies, 1998).

[10] Based on the assumption that infants were exclusively formula fed and consumed 800 mL of formula that was prepared with tap water.

Note: Insufficient data were available to estimate intake from soil or food.

Table 3: Upper-bounding estimates of intake of 2-ethoxyethanol from consumer products by adult Canadians

Consumer product	Assumptions	Estimated intake per event (mg/kg-bw per event)	Estimated average daily intake (mg/kg-bw per day)
Nail polish	**Dermal**[1] - based on the upper bound of the concentration range of 0.3–1% of 2-ethoxyethanol in nail polish (Health Canada, 1998d) - assuming a typical quantity of product used per event for "nail polish & enamel" of 0.28 g and a maximum event frequency of 0.71 times per day for users only (U.S. EPA, 1997) - a body weight of 70.9 kg is assumed for an average Canadian adult (EHD, 1998) $\frac{(0.01)\ (280\ \text{mg})\ (0.71/\text{day})}{(70.9\ \text{kg-bw})}$	0.04	0.03
All-purpose liquid cleaner	**Inhalation**[2] - based on a maximum concentration of 5% 2-ethoxyethanol in all-purpose liquid cleaner (Flick, 1986) - assuming a mass of 35 g is used per event, a 0.47-hour duration of exposure, a room volume of 20 m^3, a breathing rate of 1.3 m^3/hour for an average adult during light-level activity and a frequency of use of 360 days/year (Versar Inc., 1986) - a body weight of 70.9 kg is assumed for an average Canadian adult (EHD, 1998) $\frac{(0.05)\ (35\ 000\ \text{mg})\ (0.47\ \text{hours})\ (1.3\ \text{m}^3/\text{hour})\ (360/365\ \text{days})}{(20\ \text{m}^3)\ (70.9\ \text{kg-bw})}$	0.8 [estimated indoor air concentration of 88 mg/m^3]	0.7

Consumer product	Assumptions	Estimated intake per event (mg/kg-bw per event)	Estimated average daily intake (mg/kg-bw per day)
	Dermal[1] - based on a maximum concentration of 5% 2-ethoxyethanol in all-purpose liquid cleaner (Flick, 1986) - assuming an event frequency of 360 days/year, an exposed surface area of 400 cm^2 (both palms), a product density of 1.19 g/cm^3 and a film thickness on the hands of 2.1×10^{-3} cm (Versar Inc., 1986) - a body weight of 70.9 kg is assumed for an average Canadian adult (EHD, 1998) $\frac{(0.05)\,(360/365\ \text{days})\,(400\ \text{cm}^2)\,(1.19\ \text{g/cm}^3)\,(2.1 \times 10^{-3}\ \text{cm})\,(1000\ \text{mg/g})}{(70.9\ \text{kg-bw})}$	0.7	0.7
All-purpose spray cleaner	**Inhalation**[2] - based on a maximum concentration of 5% 2-ethoxyethanol in all-purpose spray cleaner (Flick, 1986) - assuming a mass of 76 g is used per event, a 0.47-hour duration of exposure, a room volume of 20 m^3, a breathing rate of 1.3 m^3/hour for an average adult during light-level activity and a frequency of use of 360 days/year (Versar Inc., 1986) - a body weight of 70.9 kg is assumed for an average Canadian adult (EHD, 1998) $\frac{(0.05)\,(360/365\ \text{days})\,(76\,000\ \text{mg})\,(0.47\ \text{hours})\,(1.3\ \text{m}^3/\text{hour})}{(20\ \text{m}^3)\,(70.9\ \text{kg-bw})}$	1.6 [estimated indoor air concentration of 190 mg/m^3]	1.6

Consumer product	Assumptions	Estimated intake per event (mg/kg-bw per event)	Estimated average daily intake (mg/kg-bw per day)
	Dermal[1] - based on a maximum concentration of 5% 2-ethoxyethanol in all-purpose spray cleaner (Flick, 1986) - assuming an event frequency of 360 days/year, an exposed surface area of 400 cm^2 (both palms), a product density of 0.88 g/cm^3 and a film thickness on the hands of 2.1×10^{-3} cm (Versar Inc., 1986) - a body weight of 70.9 kg is assumed for an average Canadian adult (EHD, 1998) $\frac{(0.05)\ (360/365\ days)\ (400\ cm^2)\ (0.88\ g/cm^3)\ (2.1 \times 10^{-3}\ cm)\ (1000\ mg/g)}{(70.9\ kg\text{-}bw)}$	0.5	0.5
Floor wax/polish (mop application)	**Inhalation**[2] - based on a maximum concentration of 5% 2-ethoxyethanol in floor polish (Versar Inc., 1986) - assuming a mass of 430 g is used per event, a 0.60-hour duration of exposure, a room volume of 20 m^3, a breathing rate of 1.3 m^3/hour for an average adult during light-level activity and a frequency of use of 12 days/year (Versar Inc., 1986) - a body weight of 70.9 kg is assumed for an average Canadian adult (EHD, 1998) $\frac{(0.05)\ (430\ 000\ mg)\ (0.60\ hours)\ (1.3\ m^3/hour)\ (12/365\ days)}{(20\ m^3)\ (70.9\ kg\text{-}bw)}$	12 [estimated indoor air concentration of 1075 mg/m^3]	0.4

Consumer product	Assumptions	Estimated intake per event (mg/kg-bw per event)	Estimated average daily intake (mg/kg-bw per day)
Floor wax/polish (rag application)	**Inhalation**[2] - based on a maximum concentration of 5% 2-ethoxyethanol in floor polish (Versar Inc., 1986) - assuming a mass of 430 g is used per event, a 0.60-hour duration of exposure, a room volume of 20 m^3, a breathing rate of 1.3 m^3/hour for an average adult during light-level activity and a frequency of use of 4 days/year (Versar Inc., 1986) - a body weight of 70.9 kg is assumed for an average Canadian adult (EHD, 1998) $\frac{(0.05)\,(430\,000\text{ mg})\,(0.60\text{ hours})\,(1.3\text{ m}^3/\text{hour})\,(4/365\text{ days})}{(20\text{ m}^3)\,(70.9\text{ kg-bw})}$	12 [estimated indoor air concentration of 1075 mg/m^3]	0.1
	Dermal[1] - based on a maximum concentration of 5% 2-ethoxyethanol in floor polish (Versar Inc., 1986) - assuming an event frequency of 4 days/year, an exposed surface area of 400 cm^2 (palm and fingers of two hands), a product density of 1.017 g/cm^3 and a film thickness on the hands of 2.1×10^{-3} cm (Versar Inc., 1986) - a body weight of 70.9 kg is assumed for an average Canadian adult (EHD, 1998) $\frac{(0.05)\,(4/365\text{ days})\,(400\text{ cm}^2)\,(1.017\text{ g/cm}^3)\,(2.1 \times 10^{-3}\text{ cm})\,(1000\text{ mg/g})}{(70.9\text{ kg-bw})}$	0.6	0.007

Consumer product	Assumptions	Estimated intake per event (mg/kg-bw per event)	Estimated average daily intake (mg/kg-bw per day)
Latex or oil-based paints	**Inhalation**[2] - based on a maximum concentration of 5% 2-ethoxyethyl acetate in paint (General Paint Ltd., 1997) - assuming a mass of 6130 g is used per event, a 5.5-hour duration of exposure, a room volume of 20 m^3, a breathing rate of 1.3 m^3/hour for an average adult during light-level activity and a frequency of use of 7 days/year (Versar Inc., 1986) - a body weight of 70.9 kg is assumed for an average Canadian adult (EHD, 1998) $\frac{(0.05)\,(6130\ g)\,(5.5\ hours)\,(1.3\ m^3/hour)\,(7/365)\,(1000\ mg/g)}{(20\ m^3)\,(70.9\ kg\text{-}bw)}$	1545 as the acetate [equivalent to 1053 2-ethoxyethanol] [estimated indoor air concentration of 15 325 mg 2-ethoxyethyl acetate/m^3 or 10 452 mg 2-ethoxyethanol/m^3]	30 as the acetate [equivalent to 20 2-ethoxyethanol]
	Dermal[1] - based on a maximum concentration of 5% 2-ethoxyethyl acetate in paint (General Paint Ltd., 1997) - assuming an event frequency of 7 days/year, an exposed surface area of 220 cm^2 (10% of face, hands and forearms), a film thickness on the hands of 9.81×10^{-3} cm and a product density of 1240 mg/cm^3 (Versar Inc., 1986) - a body weight of 70.9 kg is assumed for an average Canadian adult (EHD, 1998) $\frac{(0.05)\,(220\ cm^2)\,(9.81 \times 10^{-3}\ cm)\,(1240\ mg/cm^3)\,(7/365\ days)}{(70.9\ kg\text{-}bw)}$	1.9 as the acetate [equivalent to 1.3 2-ethoxyethanol]	0.04 as the acetate [equivalent to 0.03 2-ethoxyethanol]

Consumer product	Assumptions	Estimated intake per event (mg/kg-bw per event)	Estimated average daily intake (mg/kg-bw per day)
P/int thinner	**Inhalation**[2] - based on a maximum concentration of 60% 2-ethoxyethyl acetate in paint thinner (General Paint Ltd., 1997) - assuming a mass of 5430 g is used per event, a 0.5-hour duration of exposure, a room volume of 125 m^3, a breathing rate of 1.3 m^3/hour for an average adult during light-level activity and a frequency of use of 48 days/year (Versar Inc., 1986) - a body weight of 70.9 kg is assumed for an average Canadian adult (EHD, 1998) $\frac{(0.60)\ (5430\ g)\ (0.5\ hours)\ (1.3\ m^3/hour)\ (48/365\ days)\ (1000\ mg/g)}{(125\ m^3)\ (70.9\ kg\text{-}bw)}$	239 as the acetate [equivalent to 163 2-ethoxyethanol] [estimated indoor air concentration of 26 064 mg 2-ethoxyethyl acetate/m^3 or 17 776 mg 2-ethoxyethanol/m^3]	31 as the acetate [equivalent to 21 2-ethoxyethanol]
	Dermal[1] - based on a maximum concentration of 60% 2-ethoxyethyl acetate in paint thinner (General Paint Ltd., 1997) - assuming an event frequency of 48 days/year, an exposed surface area of 795 cm^2 (both hands), a film thickness on the hands of 3.25×10^{-3} cm and a product density of 0.80 g/cm^3 (Versar Inc., 1986) - a body weight of 70.9 kg is assumed for an average Canadian adult (EHD, 1998) $\frac{(0.60)\ (48/365\ days)\ (795\ cm^2)\ (3.25 \times 10^{-3}\ cm)\ (0.80\ mg/cm^3)\ (1000\ mg/g)}{(70.9\ kg\text{-}bw)}$	17 as the acetate [equivalent to 12 2-ethoxyethanol]	2.3 as the acetate [equivalent to 1.6 2-ethoxyethanol]

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[1] Estimates of intake by dermal absorption of 2-ethoxyethanol in liquid consumer products are based on the assumptions that a portion of the skin contacts the liquid and the amount absorbed is directly proportional to the area of exposed skin. It is assumed that all of the ingredient present in the liquid is absorbed through the skin. Standard exposure scenarios for dermal absorption of ingredients of liquid consumer products (e.g., Versar Inc., 1986; U.S. EPA, 1997) often include recommended skin surface areas and surface film thickness depending on the type of product and the manner in which it is used. For example, in Versar Inc. (1986), surface areas assumed are 400 cm^2 for both palms of adult hands for scenarios involving some liquid cleaning products and 220 cm^2 for the portion (i.e., 10%) of the face, hands and forearms of an average-sized adult that can potentially be covered with paint splatter during

application of latex paint. Experimental data for surface film thickness are often not available for some types of consumer products and are estimated by analogy with other liquid substances.

[2] Estimates of intake by inhalation are based on the assumptions that the ingredient is completely and instantaneously released from the applied product, the concentration is homogenous throughout the assumed volume, and no air exchange occurs between this volume and adjacent areas. Standard exposure scenarios for inhalation intakes of volatile ingredients of consumer products used in indoor spaces (e.g., Versar Inc., 1986; U.S. EPA, 1997) often include recommended room volumes intended to be representative of the areas within a residence where the products are typically used. For example, in Versar Inc. (1986), a room volume of 20 m^3 is assumed for tasks involving all-purpose liquid and spray cleaners and paints, whereas a larger volume of 125 m^3 is recommended for the use of lacquer thinner, since the task of cleaning up is assumed to take place in a basement area, rather than within a room in the house.

DRAFT FOR
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Canadian Environmental Protection Act, 1999

PRIORITY SUBSTANCES LIST

ASSESSMENT REPORT

2-BUTOXYETHANOL

Environment Canada
Health Canada

August 2000

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LIST OF ACRONYMS AND ABBREVIATIONS

AUC	area under the curve
BAA	2-butoxyacetic acid
BMC	Benchmark Concentration
CAS	Chemical Abstracts Service
CEPA	*Canadian Environmental Protection Act*
CEPA 1999	*Canadian Environmental Protection Act, 1999*
CFC	chlorofluorocarbon
CTV	Critical Toxicity Value
EEV	Estimated Exposure Value
ENEV	Estimated No-Effects Value
GWP	Global Warming Potential
HC_5	hazardous concentration to 5% of test species
K_{oc}	organic carbon sorption coefficient
K_{ow}	octanol/water partition coefficient
kg-bw	kilogram body weight
LC_{50}	median lethal concentration
LCL	lower confidence limit
LD_{50}	median lethal dose
LOAEL	Lowest-Observed-Adverse-Effect Level
LOEL	Lowest-Observed-Effect Level
NOEL	No-Observed-Effect Level
NTP	National Toxicology Program
ODP	Ozone Depletion Potential
PBPK	physiologically based pharmacokinetic
POCP	Photochemical Ozone Creation Potential
PSL	Priority Substances List
TC	Tolerable Concentration

Synopsis

2-Butoxyethanol is commercially produced in Canada and imported for use mainly as a component of formulations, as part of consumer products or manufactured articles, and as a chemical processing aid. Most reported environmental releases are to the atmosphere, with some minor releases to water.

2-Butoxyethanol reacts with hydroxyl radicals in the air with a half-life of a few hours to about a day. Most of the 2-butoxyethanol released to the atmosphere is predicted to remain in air, with some partitioning to water and soil. 2-Butoxyethanol is biodegraded in water and soil, with an estimated half-life of 1–4 weeks. It has a low octanol/water partition coefficient and is therefore not expected to bioaccumulate to any significant degree. Only limited data are available on concentrations of 2-butoxyethanol in the environment in Canada or elsewhere.

Data on toxicity were identified for aquatic organisms, including microorganisms, invertebrates and fish. The most sensitive species reported, based on acute exposure, is the grass shrimp (*Palaemonetes pugio*).

Because of the limitations of environmental monitoring data, exposures for environmental compartments other than air were estimated based on modelling. Estimated environmental concentrations of 2-butoxyethanol are a few orders of magnitude less than the adverse effects thresholds calculated for sensitive organisms.

2-Butoxyethanol is not involved in stratospheric ozone depletion and is not an important contributor to climate change or ground-level ozone formation.

Based on the limited data identified, inhalation of 2-butoxyethanol in air is an important route of exposure, with estimated exposure through use of consumer products containing the substance being considerable. No data were identified concerning the contribution of food to overall exposure to 2-butoxyethanol.

Based primarily on investigations in experimental animals, the principal critical health effects associated with exposure to 2-butoxyethanol are alterations in hematological parameters associated with hemolysis. Tolerable Concentrations for these effects and for lesions of the forestomach in mice, for which information on mode of action is inadequate to preclude their relevance to humans, were developed, based on Benchmark Concentrations. A Tolerable Concentration is the level of intake to which it is believed a person may be exposed daily over a lifetime without deleterious effect.

Levels of 2-butoxyethanol in ambient air in Canada are less than the Tolerable Concentrations derived for effects on the blood or forestomach. However, exposure to 2-butoxyethanol during use of products containing the substance could potentially greatly exceed the Tolerable Concentrations, based on limited data on emissions from products currently available in Canada.

Based on available data, it is proposed that 2-butoxyethanol is not entering the environment in a quantity or concentration or under conditions that have or may have an immediate or long-term harmful effect on the environment or its biological diversity; or constitute or may constitute a danger to the environment on which life depends. 2-Butoxyethanol is considered to be entering the environment in a quantity or concentration or under conditions that constitute or may constitute a danger in Canada to human life or health. Therefore, it is proposed that 2-butoxyethanol be considered to be "toxic" as defined in Section 64 of CEPA 1999.

Additional characterization of the ranges and distributions of concentrations of 2-butoxyethanol in consumer products currently available in Canada and their emissions is considered a clear priority as a basis for risk management.

1.0 INTRODUCTION

The *Canadian Environmental Protection Act, 1999* (CEPA 1999) requires the federal Ministers of the Environment and of Health to prepare and publish a Priority Substances List (PSL) that identifies substances, including chemicals, groups of chemicals, effluents and wastes, that may be harmful to the environment or constitute a danger to human health. The Act also requires both Ministers to assess these substances and determine whether they are "toxic" or capable of becoming "toxic" as defined in Section 64 of the Act, which states:

> ...a substance is toxic if it is entering or may enter the environment in a quantity or concentration or under conditions that
> (a) have or may have an immediate or long-term harmful effect on the environment or its biological diversity;
> (b) constitute or may constitute a danger to the environment on which life depends; or
> (c) constitute or may constitute a danger in Canada to human life or health.

Substances that are assessed as "toxic" as defined in Section 64 may be placed on Schedule I of the Act and considered for possible risk management measures, such as regulations, guidelines, pollution prevention plans or codes of practice to control any aspect of their life cycle, from the research and development stage through manufacture, use, storage, transport and ultimate disposal.

Based on initial screening of readily accessible information, the rationale for assessing 2-butoxyethanol (along with 2-methoxyethanol and 2-ethoxyethanol) provided by the Ministers' Expert Advisory Panel on the Second Priority Substances List (Ministers' Expert Advisory Panel, 1995) was as follows:

> Potential sources of exposure to these compounds include releases from various industrial and consumer uses. These compounds are widely used as solvents in paints and protective coatings; in printing inks, industrial solvents and cleaners; in the production of plasticizers; as a de-icer in fuels and automotive brake fluids; and in electronics manufacturing. Effects due to exposure include disorders of the central nervous system, blood system, kidneys and liver in both humans and animals. An assessment is required to determine the presence of these substances in the Canadian environment, exposure and the potential risks to human health.

Descriptions of the approaches to assessment of the effects of Priority Substances on the environment and human health are available in published companion documents. The document entitled "Environmental Assessments of Priority Substances under the *Canadian Environmental Protection Act*. Guidance Manual Version 1.0 — March 1997" (Environment Canada, 1997a) provides guidance for conducting environmental assessments of Priority Substances in Canada. This document may be purchased from:

Environmental Protection Publications
Environmental Technology Advancement Directorate
Environment Canada
Ottawa, Ontario
K1A 0H3

It is also available on the Commercial Chemicals Branch web site at www.ec.gc.ca/cceb1/eng/psap.htm under the heading "Technical Guidance Manual." It should be noted that the approach outlined therein has evolved to incorporate recent developments in risk assessment methodology, which will be addressed in future releases of the guidance manual for environmental assessments of Priority Substances.

The approach to assessment of effects on human health is outlined in the following publication of the Environmental Health Directorate of Health Canada: "*Canadian Environmental Protection Act* — Human Health Risk Assessment for Priority Substances" (Health Canada, 1994), copies of which are available from:

Environmental Health Centre
Room 104
Health Canada
Tunney's Pasture
Ottawa, Ontario
K1A 0L2

or on the Environmental Health Directorate publications web site (www.hc-sc.gc.ca/ehp/ehd/catalogue/bch.htm). The approach is also described in an article published in the *Journal of Environmental Science and Health — Environmental Carcinogenesis & Ecotoxicology Reviews* (Meek *et al*., 1994). It should be noted that the approach outlined therein has evolved to incorporate recent developments in risk assessment methodology, which are described on the Environmental Substances Division web site (www.hc-sc.gc.ca/ehp/ehd/bch/env_contaminants/psap/psap.htm) and which will be addressed in future releases of the approach paper for the assessment of effects on human health.

The search strategies employed in the identification of data relevant to the assessment of entry, environmental fate and exposure, and potential effects on the environment (prior to October 1999) as well as assessment of potential human exposure and health effects (prior to October 1999) are presented in Appendix A. Review articles were consulted where appropriate. However, all original studies that form the basis for determining whether 2-butoxyethanol is "toxic" under CEPA 1999 have been critically evaluated by staff of Environment Canada (entry and environmental exposure and effects) and Health Canada (human exposure and effects on human health).

Sections of the Assessment Report related to the environmental assessment of 2-butoxyethanol and the environmental Supporting Document (Environment Canada, 1999) were prepared or reviewed by the following members of the Environmental Resource Group, established by Environment Canada to support the environmental assessment:

D. Boersma, Environment Canada
R. Breton, Environment Canada
P. Cureton, Environment Canada
N. Davidson, Environment Canada
R. Desjardins, Environment Canada
L. Hamel, Union Carbide Canada Inc.
B. Lee, Environment Canada
S. Lewis, Chemical Manufacturers' Association
B. Sebastien, Environment Canada
K. Taylor, Environment Canada (lead for the environmental assessment)

Sections of the Assessment Report relevant to the environmental assessment and the environmental Supporting Document were also reviewed by C. Staples (Assessment Technologies Inc.).

A summary of data relevant to assessment of the potential risk to human health associated with exposure to 2-butoxyethanol was prepared in 1996 by BIBRA Toxicology International. Additional recent reviews were also used for the identification of relevant data, including those prepared for the International Programme on Chemical Safety (IPCS, 1998) and the Agency for Toxic Substances and Disease Registry (ATSDR, 1998). Additional and more recent data have been identified through searching the on-line databases listed in Appendix A.

Sections of the Assessment Report related to human health and the relevant supporting documentation were prepared by the following staff of Health Canada:

K. Hughes
M.E. Meek
D. Moir
L. Turner
M. Walker

H. Atkins (Ottawa Hospital, General Campus) provided advice on the biological significance of hematological effects. A. Renwick (University of Southampton) provided advice on the adequacy of data as a basis for replacement of default components of uncertainty factors. Input on this aspect was also received at a workshop of the International Programme on Chemical Safety on uncertainty and variability in risk assessment, held in Berlin, Germany, on May 9–11, 2000.

Comments primarily on the adequacy of coverage in the sections of the supporting documentation related to health effects were provided in a written review by members of the Canadian Manufacturers' Association Ethylene Glycol Ethers Panel, including:

R. Boatman, Eastman Kodak (for Eastman Chemical)
R. Gingell, Shell Chemical
S. Lewis, Canadian Manufacturers' Association
A. Schumann, Dow Chemical
T. Tyler, Union Carbide Corporation

Comments on accuracy of reporting, adequacy of coverage and defensibility of conclusions with respect to hazard characterization were provided in written review by BIBRA International and H. Atkins (Ottawa Hospital, General Campus).

Accuracy of reporting, adequacy of coverage and defensibility of conclusions with respect to hazard characterization and exposure–response analyses were considered in written review of the completed Assessment Report by:

H. Clewell, K.S. Crump Group, Inc., ICF Kaiser International, Inc.
J. Delic, U.K. Health and Safety Executive
J. Gift, National Center for Environmental Assessment, U.S. Environmental Protection Agency
J. Roycoft, National Institute for Environmental Health Sciences

The health-related sections of the Assessment Report were reviewed and approved by the Health Protection Branch Risk Management meeting of Health Canada.

The entire Assessment Report was reviewed and approved by the Environment Canada/Health Canada CEPA Management meeting.

The text of the Assessment Report has been structured to address environmental effects initially (relevant to determination of "toxic" under Paragraphs 64(a) and (b)), followed by effects on human health (relevant to determination of "toxic" under Paragraph 64(c)).

Copies of this Assessment Report are available upon request from:

Inquiry Centre
Environment Canada
Main Floor, Place Vincent Massey
351 St. Joseph Blvd.
Hull, Quebec
K1A 0H3

or on the Internet at:

www.ec.gc.ca/cceb1/eng/public/index_e.html

Unpublished supporting documentation, which presents additional information, is available upon request from:

Commercial Chemicals Evaluation Branch
Environment Canada
14th Floor, Place Vincent Massey
351 St. Joseph Blvd.
Hull, Quebec
K1A 0H3

or

Environmental Health Centre
Room 104
Health Canada
Tunney's Pasture
Ottawa, Ontario
K1A 0L2

2.0 SUMMARY OF INFORMATION CRITICAL TO ASSESSMENT OF "TOXIC" UNDER CEPA 1999

2.1 Identity and physical/chemical properties[1]

2-Butoxyethanol has the empirical molecular formula $C_6H_{14}O_2$, the structural formula $CH_3CH_2CH_2CH_2OCH_2CH_2OH$ and a molecular weight of 118.2. Its Chemical Abstracts Service (CAS) Registry Number is 111-76-2. 2-Butoxyethanol is a colourless liquid with a water solubility of 63 500 mg/L at 25°C, an octanol/water partition coefficient (log K_{ow}) of 0.84, a vapour pressure of 296 Pa at 25°C and a calculated Henry's law constant of 0.551 $Pa{\cdot}m^3/mol$ (ASTER, 1996). The conversion factor for air is 1 ppm = 4.83 mg/m^3.

Synonyms for 2-butoxyethanol include 2-butoxy-1-ethanol; ethylene glycol, monobutyl ether; and butyl cellosolve.

2.2 Entry characterization

2.2.1 Production, importation and uses

According to data reported to Environment Canada from 188 companies through a survey carried out under the authority of Section 16 of the 1988 *Canadian Environmental Protection Act* (CEPA), Canadian production of 2-butoxyethanol was 182.7 tonnes in 1995 and 235.3 tonnes in 1996. Importation of 2-butoxyethanol into Canada was 6.5 kilotonnes in 1995 and 7.2 kilotonnes in 1996. Exports of 2-butoxyethanol totalled 35.9 tonnes in 1995 and 34.3 tonnes in 1996 (Environment Canada, 1997b). Statistics Canada (1997) reported that 4.3 kilotonnes of 2-butoxyethanol were imported in 1995, whereas 2.2 kilotonnes were imported in 1996.

2-Butoxyethanol has been used in paints, coatings, inks, cleaners, polishes, brake fluids and jet fuels and has been widely used as a solvent, chemical intermediate and solvent coupler of mixtures and water-based formulations (Stemmler *et al*., 1997). It is used as a solvent in surface coatings, such as spray lacquers, quick-dry lacquers, enamels, varnishes and latex paint, as well as in varnish removers; as a coupling agent in metal cleaning formulas and household cleaners; and as a component in herbicides and automotive brake fluids (U.S. Department of Health and Human Services, 1990). It has also been used as an ice fog suppressant (U.S. EPA, 1979).

In a CEPA Section 16 survey of 188 companies, it was reported that 4.4 kilotonnes of 2-butoxyethanol were used in Canada in 1995 and 5.2 kilotonnes in 1996, mainly as a component of formulations, as part of consumer products or manufactured articles, or as a chemical processing aid (Environment Canada, 1997b).

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[1] See the environmental Supporting Document (Environment Canada, 1999) for a more complete listing of ranges of values reported and criteria for selection of physical and chemical properties.

2-Butoxyethanol is present in approximately 73 pesticides currently registered for use in Canada, but not in those expected to be used on food commodities. It is used in domestic insecticides, pet sprays, bear/dog deterrents and pesticides used for cleaning/disinfecting purposes and to control aquatic weeds (Health Canada, 1998c).

2.2.2 Sources and releases

2.2.2.1 Natural sources

No information has been found to indicate that 2-butoxyethanol occurs as a natural product. There are no known reactions that would lead to the *in situ* production of 2-butoxyethanol or other glycol ethers in the atmosphere (Rogozen *et al.*, 1987).

2.2.2.2 Anthropogenic sources

Information about 2-butoxyethanol was not available from the National Pollutant Release Inventory, because the substance was added to the inventory only in 1999.

According to data reported under the CEPA Section 16 survey, 249 tonnes of 2-butoxyethanol were released into the air in Canada in 1996, while 63 tonnes were released as waste, 6.5 tonnes were released into landfills and 2 tonnes were released into water (Environment Canada, 1997b).

The Canadian Chemical Producers' Association (1997) reported total environmental emissions of 2-butoxyethanol of 1.0, 3.0, 2.0 and 1.0 tonnes by member companies in 1992, 1993, 1994 and 1995, respectively, all of which were released to air. Reported emissions totalled 1.0 tonne in 1996, 2.0 tonnes in 1997 and 1.0 tonne in 1998 (Canadian Chemical Producers' Association, 1999a,b).

2-Butoxyethanol was detected at a concentration of 0.23 $\mu g/m^3$ in the emissions of a municipal waste incineration plant in Germany (Jay and Stieglitz, 1995).

Leachate from municipal landfills and hazardous waste sites can release 2-butoxyethanol to groundwater (Brown and Donnelly, 1988; Howard, 1993). Concentrations of 2-butoxyethanol in aqueous samples from a municipal and an industrial landfill in the United States ranged from <0.4 to 84 mg/L (Beihoffer and Ferguson, 1994).

2.3 Exposure characterization

2.3.1 Environmental fate

2.3.1.1 Air

In air, 2-butoxyethanol is expected to exist almost entirely in the vapour phase, and reactions with photochemically produced hydroxyl radicals should be important. Tuazon *et al.* (1998) reported that the gas-phase reaction products of 2-butoxyethanol with hydroxyl radicals in the presence of nitric oxide were n-butyl formate, 2-hydroxyethyl formate, propanal, 3-hydroxybutyl formate, an organic nitrate and one or more hydroxycarbonyl products. Stemmler *et al.* (1997) irradiated synthetic air mixtures containing 2-butoxyethanol, methyl nitrite and nitric oxide in a Teflon bag reactor at room temperature. The major oxidation products were butyl formate, ethylene glycol monoformate, butoxyacetaldehyde, 3-hydroxybutyl formate and propionaldehyde, whereas minor products were 2-propyl-1,3-dioxolane, ethylene glycol monobutyrate, 2-hydroxybutyl formate, acetaldehyde, propyl nitrate and butyraldehyde. Physical removal of 2-butoxyethanol from air by precipitation and dilution in clouds may occur; however, its short atmospheric residence time indicates that wet deposition is of limited importance (Howard, 1993). Howard *et al.* (1991) estimated a half-life of 2-butoxyethanol in air of 3.28–32.8 hours, based on photooxidation.

2.3.1.2 Water

The estimated half-life of 2-butoxyethanol in surface water is 1–4 weeks, based on aerobic biodegradation rates (Howard *et al.*, 1991). Because of its low log K_{ow} and Henry's law constant, adsorption to particulates and volatilization from surface water are not expected to be important fate processes for 2-butoxyethanol (SIDS, 1996).

Because of its low organic carbon sorption coefficient (K_{oc}), 2-butoxyethanol should be highly mobile in soil and potentially could reach groundwater if released into soil (SIDS, 1996). Howard *et al.* (1991) estimated a half-life of 2-butoxyethanol in groundwater of 2–8 weeks, based on unacclimated aqueous aerobic biodegradation.

2.3.1.3 Soils

Howard *et al.* (1991) estimated a half-life of 2-butoxyethanol in soil of 1–4 weeks, based on unacclimated aqueous aerobic biodegradation.

2.3.1.4 Biota

A bioconcentration factor of 2.5 was calculated for 2-butoxyethanol (SRC, 1988). Bioaccumulation of 2-butoxyethanol in aquatic organisms would therefore not be significant.

2.3.1.5 Environmental distribution

A Level III fugacity model was used to estimate the environmental partitioning of 2-butoxyethanol when released into air, water or soil. Values for input parameters were as follows: molecular weight, 118 g/mol; vapour pressure, 296 Pa; water solubility, 63 500 mg/L; log K_{ow}, 0.84; Henry's law constant, 0.551 $Pa \cdot m^3/mol$; half-life[2] in air, 17 hours; half-life in water, 550 hours; half-life in soil, 550 hours; and half-life in sediment, 1700 hours. Modelling was based upon an assumed emission rate of 1000 kg per hour, although the emission rate used would not affect the estimated percent distribution. If 2-butoxyethanol is emitted into air, EQC (Equilibrium Criterion) Level III fugacity modelling predicts that about 66% would be present in air, about 20% in water and about 14% in soil. If 2-butoxyethanol is emitted into water, more than 99% would be present in water. If 2-butoxyethanol is released to soil, about 75% would be present in soil and about 25% in water.

2.3.2 Environmental concentrations

Few data on levels of 2-butoxyethanol in the environment have been identified for Canada or elsewhere. One study was conducted to determine concentrations of 2-butoxyethanol in multiple media to which humans are exposed in Canada, including drinking water and indoor and outdoor air (Conor Pacific Environmental Technologies Inc., 1998), as outlined below in Section 2.3.2.1. Additional data on levels of 2-butoxyethanol in specific media are presented in the subsequent sections.

2.3.2.1 Multimedia exposure study

In a Canadian multimedia study, exposure to a number of volatile organic chemicals was measured for 50 participants across Canada (Conor Pacific Environmental Technologies Inc., 1998). Thirty-five participants were randomly selected from the Greater Toronto area in Ontario, six from Queens Subdivision in Nova Scotia and nine from Edmonton, Alberta. For each participant, samples of drinking water, beverages and indoor, outdoor and personal air were collected over a 24-hour period. (It should be noted that confidence in the results of this survey is low, due to limitations of the analytical methods involved, as discussed in Section 3.3.5.) Samples of foods were not analysed for 2-butoxyethanol.

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[2] For each environmental compartment, DMER and AEL (1996) use a series of ranges of half-life times (<10 hours, 10–30 hours, 30–100 hours, etc.), and the half-life of the particular substance is assigned to the appropriate range, based on a consideration of available persistence data. The geometric mean of this range is then used as an input parameter for the fugacity model. For example, the atmospheric half-life of 2-butoxyethanol in air is judged to be between 10 and 30 hours. The geometric mean of this range, 17 hours, is used as an input parameter in the model. Conservative values for persistence were selected, i.e., longer rather than shorter half-lives, to ensure that persistence is not underestimated.

In outdoor air, levels of 2-butoxyethanol were above the limit of detection (0.84 µg/m^3) in 32% of the 50 samples. Concentrations of 2-butoxyethanol ranged from below the limit of detection to 243 µg/m^3, with a mean concentration[3] of 8.4 µg/m^3. In indoor air, 2-butoxyethanol was detected in 66% of the 50 samples (detection limit 0.84 µg/m^3). The concentration of 2-butoxyethanol ranged from below the limit of detection to 438 µg/m^3, with a mean value of 27.5 µg/m^3. 2-Butoxyethanol was detected in 70% of the 50 personal air samples (detection limit 0.84 µg/m^3). Concentrations ranged from below the limit of detection to 275 µg/m^3, with a mean concentration of 31 µg/m^3.

2-Butoxyethanol was detected in 68% of the 50 drinking water samples (detection limit 0.02 µg/L). Concentrations ranged from below the limit of detection to 0.94 µg/L, with a mean concentration of 0.18 µg/L. 2-Butoxyethanol was detected in 56% of the 50 beverage samples (detection limit 6.80 µg/L). Concentrations ranged up to 73.8 µg/L, and the mean concentration was 6.46 µg/L.

2.3.2.2 Ambient air

In the Windsor Air Quality Study, the concentrations of 2-butoxyethanol in 24 samples of ambient air collected in the vicinity of an automotive plant and in 7 samples collected in downtown Windsor were measured. Concentrations of 2-butoxyethanol were less than the limit of detection (3.3 µg/m^3) in all the samples collected in downtown Windsor. Of the 24 samples collected at the automotive plant, concentrations of 2-butoxyethanol were above the limits of detection (which ranged from 0.65 to 1.3 µg/m^3) in 16 (67%); the mean value for these samples was 2.3 µg/m^3, when concentrations in samples where 2-butoxyethanol was not detected were assumed to be equivalent to one-half the limit of detection, and the maximum concentration was 7.3 µg/m^3. The authors stated that the probable source of 2-butoxyethanol in ambient air samples downwind of the plant was from paints and lacquers in which 2-butoxyethanol is used as a solvent (OMEE, 1994).

In samples of ambient air collected between 1990 and 1993 in countries other than Canada, concentrations of 2-butoxyethanol ranged from below the limits of detection to 21 ppb (101 µg/m^3) (Ciccioli *et al.*, 1993, 1996; Daisey *et al.*, 1994; Brinke, 1995; Shields *et al.*, 1996). 2-Butoxyethanol has also been quantified in air from Terra Nova Bay, Antarctica, at concentrations ranging from 1.2 to 14 µg/m^3 (Ciccioli *et al.*, 1996).

2.3.2.3 Indoor air

In samples of indoor air collected in homes in Italy, concentrations of 2-butoxyethanol ranged from below the limit of detection (not specified) to 8 µg/m^3 (De Bortoli *et al.*, 1986). Concentrations of up to

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[3] In all outdoor air, indoor air, personal air, drinking water and beverage samples where 2-butoxyethanol was not detected, concentrations were assumed to be equivalent to one-half the limit of detection for the calculation of the mean concentration.

130 μg/m^3 were measured in indoor air in office buildings in the United States (Daisey *et al.*, 1994; Shields *et al.*, 1996).

2.3.2.4 Surface water

Water samples taken from a polluted river in Japan in 1980 contained 2-butoxyethanol at a concentration of 1.31–5.68 mg/L (Yasuhara *et al.*, 1981).

2.3.2.5 Groundwater

No data were identified on the concentration of 2-butoxyethanol in groundwater in Canada or elsewhere.

2.3.2.6 Drinking water

In 29 samples of drinking water collected between 1989 and 1995 from four sites in Ontario, concentrations of 2-butoxyethanol were above the limit of detection (not specified) in one sample from each site (i.e., in 9–17% of total samples at each site). The highest concentration (5.0 μg/L) was measured in a sample collected in Port Dover (OMEE, 1996).

2.3.2.7 Soil

No data were identified on the concentration of 2-butoxyethanol in soil in Canada or elsewhere.

2.3.2.8 Food

Data on the levels of 2-butoxyethanol in food were not identified; however, 2-butoxyethanol was detected but not quantified in a sample of paper and paperboard food packaging materials in the United Kingdom (Castle *et al.*, 1997).

2.3.2.9 Consumer products

2-Butoxyethanol is used as a solvent in a number of consumer products, including paints, paint thinners and cleaning products. In Canada, there are no regulations concerning permissible levels of glycol ethers, including 2-butoxyethanol, in consumer products (Health Canada, 1998a). Material Safety Data Sheets list the percent contents of 2-butoxyethanol as up to 5% in latex paints and up to 30% in paint thinners (General Paint Ltd., 1997). Of the cosmetic products currently registered for sale in Canada, 2-butoxyethanol is a registered component in 31 products at concentrations in the range of 3–10% and in 33 products at concentrations of 0.1% or less. These products include hair dyes, nail polish and nail polish removers (Health Canada, 1998b). (The *Food and Drugs Act* stipulates that manufacturers and importers of new cosmetic products are required to notify Health Canada concerning the ingredients.)

2-Butoxyethanol is present in approximately 73 pesticides currently registered for use in Canada (see Section 2.2.1).

2-Butoxyethanol concentrations of up to 20% were reported in various cleaning products, including degreasers, polishes and windshield washer fluid, used in the United States (Flick, 1986, 1989). "Low-pollutant" paints contained up to 6% 2-butoxyethanol in a study conducted in Germany (Plehn, 1990). Industrial window cleaners used in France were reported to contain 0.9–21.2% 2-butoxyethanol (Vincent *et al.*, 1993).

Emissions of 2-butoxyethanol from 13 consumer products purchased in the Ottawa, Ontario, area were recently investigated by Health Canada (Cao, 1999). Products selected were those that were believed most likely to contain 2-butoxyethanol, on the basis of other data presented here. 2-Butoxyethanol was detected in emissions from seven products, including cleaners, nail polish remover and hair colorant, at rates of up to 1186 mg/m^2 per hour.

2.3.2.10 Fugacity modelling

ChemCAN v. 4.0 modelling was used to estimate environmental concentrations of 2-butoxyethanol. This model is a Level III fugacity-based regional model developed to estimate the environmental fate of chemicals in Canada. ChemCAN calculates the distribution of chemicals in the environmental media, the rates of transport and transformation processes, and average concentrations in any of 24 regions or ecozones of Canada. The highest reported recent release of 2-butoxyethanol in Canada is 249 tonnes, released into the air by facilities in British Columbia, Ontario and Quebec in 1996, according to a survey conducted under the authority of Section 16 of CEPA (Environment Canada, 1997b). To make a conservative estimate of environmental concentrations of 2-butoxyethanol, it was assumed, for modelling purposes, that all of this was released into southern Ontario. "Ontario – Mixed Wood Plain" was therefore selected as the geographic region for ChemCAN modelling of 2-butoxyethanol. The input rate was 28.4 kg 2-butoxyethol per hour, all to the atmosphere. Chemical input values were as follows: molecular weight, 118 g/mol; vapour pressure, 296 Pa; water solubility, 63 500 mg/L; log K_{ow}, 0.84; Henry's law constant, 0.551 Pa·m^3/mol; half-life in air, 17 hours; half-life in water, 550 hours; half-life in soil, 550 hours; and half-life in sediment, 1700 hours. For Ontario – Mixed Wood Plain, environmental characteristics were as follows: total surface area, 169 000 km^2; percentage of area covered by water, 43.8%; average air height, 2 km; average water depth, 20 m; average soil depth, 10 cm; residence time in air, 1.71 days; residence time in water, 618 days; environmental temperature, 7.4°C.

Environmental concentrations of 2-butoxyethanol in southern Ontario predicted by ChemCAN v. 4.0 modelling are as follows: 1.267 ng/m^3 in air; 2.36×10^{-4} µg/L in water; 3.34×10^{-3} ng/g dry weight in soil; and 1.28×10^{-4} ng/g dry weight in sediments. The ChemCAN model estimates average concentrations throughout the region; therefore, actual concentrations in the vicinity of releases will be higher than those estimated by the model.

2.4 Effects characterization

2.4.1 Ecotoxicology

2.4.1.1 Terrestrial organisms

No information on the effects of 2-butoxyethanol on wildlife was identified. Based on the results of inhalation studies presented in Section 2.4.3, the species that were most sensitive to airborne 2-butoxyethanol were rats and mice. In subchronic toxicity tests, alterations in hematological parameters indicative of hemolytic anemia were observed in female rats and mice at the lowest concentration tested, 31 ppm (150 mg/m^3) (NTP, 1998). Hemolytic anemia was also noted in rats exposed to 31.2 ppm (151 mg/m^3) 2-butoxyethanol in a 2-year bioassay (NTP, 1998).

2.4.2 Aquatic organisms

Chronic toxicity data have been identified for protozoans, algae and fish. The most sensitive organism was the blue-green alga, *Microcystis aeruginosa*, with an 8-day toxicity threshold of 35 mg/L for inhibition of growth (Bringmann and Kuehn, 1978). Acute toxicity data have been reported for protozoans, invertebrates and fish. The most sensitive organisms were the grass shrimp (*Palaemonetes pugio*), with a 96-hour LC_{50} of 5.4 mg/L (Biospherics Inc., 1981a), and the mummichog (*Fundulus heteroclitus*), with a 96-hour LC_{50} of 6.7 mg/L (Biospherics Inc., 1981b). These values are much lower than reported values for other organisms. The next most sensitive invertebrate was the oyster (species not stated), with a 96-hour LC_{50} of 89 mg/L (U.S. EPA, 1984). The most sensitive fish species was the bluegill (*Lepomis macrochirus*), with a 96-hour LC_{50} of 127 mg/L (CIBA-GEIGY Corp., 1979), although other authors reported much higher values for this species, as presented in Table 11 of Environment Canada (1999).

2.4.2 Abiotic atmospheric effects

Worst-case calculations were made to determine if 2-butoxyethanol has the potential to contribute to depletion of stratospheric ozone, ground-level ozone formation or climate change (Bunce, 1996).

The Ozone Depletion Potential (ODP) is 0, as 2-butoxyethanol is not a halogenated compound.

The Photochemical Ozone Creation Potential (POCP) was estimated to be 70 (relative to the reference compound ethene, which has a POCP of 100), based on the following formula:

$$\text{POCP} = (k_{\text{2-butoxyethanol}}/k_{\text{ethene}}) \times (M_{\text{ethene}}/M_{\text{2-butoxyethanol}}) \times 100$$

where:

- $k_{2\text{-butoxyethanol}}$ is the rate constant for the reaction of 2-butoxyethanol with OH radicals (2.5×10^{-11} cm^3/mol per second),
- k_{ethene} is the rate constant for the reaction of ethene with OH radicals (8.5×10^{-12} cm^3/mol per second),
- M_{ethene} is the molecular weight of ethene (28.1 g/mol), and
- $M_{2\text{-butoxyethanol}}$ is the molecular weight of 2-butoxyethanol (118 g/mol).

The Global Warming Potential (GWP) was calculated to be 3.1×10^{-5} (relative to the reference compound CFC-11, which has a GWP of 1), based on the following formula:

$$GWP = (t_{2\text{-butoxyethanol}}/t_{CFC\text{-}11}) \times (M_{CFC\text{-}11}/M_{2\text{-butoxyethanol}}) \times (S_{2\text{-butoxyethanol}}/S_{CFC\text{-}11})$$

where:

- $t_{2\text{-butoxyethanol}}$ is the lifetime of 2-butoxyethanol (0.0016 years),
- $t_{CFC\text{-}11}$ is the lifetime of CFC-11 (60 years),
- $M_{CFC\text{-}11}$ is the molecular weight of CFC-11 (137.5 g/mol),
- $M_{2\text{-butoxyethanol}}$ is the molecular weight of 2-butoxyethanol (118 g/mol),
- $S_{2\text{-butoxyethanol}}$ is the infrared absorption strength of 2-butoxyethanol (2389/cm^2 per atmosphere, default), and
- $S_{CFC\text{-}11}$ is the infrared absorption strength of CFC-11 (2389/cm^2 per atmosphere).

These figures suggest that 2-butoxyethanol does not contribute to stratospheric ozone depletion, its potential contribution to climate change is negligible, and its potential contribution to ground-level ozone formation is moderate. The magnitude of these effects would depend on the concentrations of 2-butoxyethanol in the atmosphere, which are estimated to be very low in Canada. 2-Butoxyethanol's contribution to ozone formation is therefore considered negligible compared with those of other more abundant smog-forming substances, such as the reference compound, ethene (Bunce, 1996).

2.4.3 *Experimental animals and* in vitro

2.4.3.1 Kinetics and metabolism

2-Butoxyethanol is rapidly absorbed following oral, inhalation and dermal exposure. Once absorbed, it is rapidly and extensively distributed throughout the body and rapidly eliminated principally in the urine as metabolites and exhaled as carbon dioxide (thus, there is little potential for bioaccumulation). It is metabolized in the liver primarily via alcohol and aldehyde dehydrogenases to 2-butoxyacetaldehyde and 2-butoxyacetic acid (BAA, the principal and putatively active metabolite, representing up to 75% of the absorbed dose). BAA may be subsequently detoxified through conjugation (at least with glutamine in humans, but possibly not in rats) or metabolized to carbon dioxide. Comparatively minor pathways of 2-butoxyethanol metabolism result in the formation of other urinary metabolites, including glucuronide and sulphate conjugates (at least in rats) and ethylene glycol.

Although data are limited, the acetate moiety of 2-butoxyethanol (2-butoxyethyl acetate) appears to be rapidly hydrolysed to 2-butoxyethanol via esterases in several tissues in the body (Johanson, 1988). For this reason, data on the toxicity of 2-butoxyethyl acetate have been included in this assessment.

2.4.3.2 Acute toxicity

Based on LD_{50}s and LC_{50}s, 2-butoxyethanol and its acetate are of low to moderate toxicity to experimental animals following acute exposure. Hematological effects, as well as effects on the liver, kidney, lung and spleen, some of which may be secondary to hematotoxicity, have been observed in animals acutely exposed to lower doses or concentrations. For example, alterations in hematological parameters characteristic of hemolytic anemia have been observed in rats administered single oral doses as low as 125 mg/kg-bw, while hemoglobinuria was noted in older rats following gavage administration of 32 mg/kg-bw (Ghanayem *et al.*, 1987). Exposure to airborne concentrations of 62 ppm (299 mg/m^3) for 4 hours resulted in increased osmotic fragility of erythrocytes (Carpenter *et al.*, 1956), whereas dermal exposure to 260 mg/kg-bw for 6 hours induced hemolysis in rats (Bartnik *et al.*, 1987). Ghanayem *et al.* (1992) and Sivarao and Mehendale (1995) demonstrated that younger blood cells were more resilient to 2-butoxyethanol-induced hemolysis than were older cells, as rats that had been bled several days prior to exposure to a single oral dose were less severely affected than non-bled rats.

2-Butoxyethanol and its acetate are considered to be mildly to severly irritant to the skin and eyes, with the severity increasing with duration of exposure (Carpenter and Smyth, 1946; Smyth *et al.*, 1962; Truhaut *et al.*, 1979; Union Carbide, 1980; Jacobs *et al.*, 1989; Kennah *et al.*, 1989; Rohm and Haas, 1989; Jacobs, 1992; Zissu, 1995).

2.4.3.3 Short-term toxicity

Hematological effects appear to be the most sensitive endpoint in experimental animals following short-term exposure to 2-butoxyethanol by inhalation, ingestion or dermal contact, with rats being more sensitive than mice or rabbits. Hematological changes characteristic of hemolysis (including reductions in the red blood cell count, hemoglobin levels and hematocrit values) have been reported by a number of investigators in rats exposed repeatedly to 2-butoxyethanol for 2–65 days (Grant *et al.*, 1985; Krasavage, 1986; NTP, 1989; Dieter *et al.*, 1990; Ghanayem *et al.*, 1992). In most of those studies in which hematological parameters were measured, these changes were observed at all doses administered by gavage or in the drinking water (i.e., ≥100 mg/kg-bw per day); in only one study in rats exposed for only 3 days (which was designed primarily to investigate developmental toxicity) was a No-Observed-Effect Level (NOEL) of 30 mg/kg-bw per day determined (NTP, 1989). In several of these short-term studies in rats, the hematological changes appeared to be reversible after cessation of exposure (Grant *et al.*, 1985; NTP, 1989; Ghanayem *et al.*, 1992), while in other studies it appeared that tolerance or autoprotection developed in rats repeatedly exposed to 2-butoxyethanol, based on the lessening in severity of effects (Ghanayem *et al.*, 1992; Sivarao and Mehendale, 1995). In general, mice appear to be less sensitive to 2-butoxyethanol-induced hematological effects than rats. At oral doses of 500 mg/kg-bw per day or more, the only effect observed on the blood in mice was a reduction in red blood cell count (Nagano *et al.*, 1979, 1984).

Effects on other organs, including the spleen, liver and kidneys, have also been observed in rats exposed to 2-butoxyethanol, although generally only at doses or concentrations greater than those associated with alterations in hematological parameters. For example, in two studies, changes in relative weights were noted in rats administered oral doses of 100 mg/kg-bw per day or more for 3 days (NTP, 1989) or 125 mg/kg-bw per day for 12 days (Ghanayem *et al.*, 1992); however, no effects on organ weights were observed in rats administered higher doses for longer durations (Dieter *et al.*, 1990; Exon *et al.*, 1991; NTP, 1993). Similarly, increased weights of spleen and kidney were noted in rats exposed to 200 ppm (966 mg/m^3) 2-butoxyethanol via inhalation (Tyl *et al.*, 1984). In mice, decreased relative thymus weights were noted following administration of doses of 370 mg/kg-bw per day or more (NTP, 1993).

In inhalation studies, hematological changes were noted in rats exposed to 2-butoxyethanol for up to about 30 days at concentrations of 86 ppm (415 mg/m^3) or more, but not at 50 ppm (242 mg/m^3) or lower concentrations (Carpenter *et al.*, 1956; Dodd *et al.*, 1983; Tyl *et al.*, 1984). A reversible increase in erythrocyte fragility was observed in mice exposed to 100 ppm (483 mg/m^3) or higher concentrations, with transient hemoglobinuria being observed at 200 ppm (966 mg/m^3) or more (Carpenter *et al.*, 1956). Indications of hemoglobinuria were also observed in rabbits exposed to 200 ppm (966 mg/m^3) 2-butoxyethanol or 400 ppm 2-butoxyethyl acetate (2616 mg/m^3, equivalent to 1936 mg 2-butoxyethanol/m^3) (Truhaut *et al.*, 1979; Tyl *et al.*, 1984). Alterations in blood parameters were also noted in limited earlier investigations in dogs and monkeys exposed via inhalation, but not in guinea pigs (Carpenter *et al.*, 1956). Non-hematological effects observed in inhalation studies included an increase in weights of spleen and kidney in rats exposed to 200 ppm (966 mg/m^3) 2-butoxyethanol (Tyl *et al.*, 1984) and histopathological changes in the kidney in rabbits exposed to 400 ppm 2-butoxyethyl acetate (2616 mg/m^3, equivalent to 1936 mg 2-butoxyethanol/m^3) (Truhaut *et al.*, 1979).

Alterations in blood parameters were also observed in an earlier investigation in rabbits repeatedly administered 180 mg 2-butoxyethanol/kg-bw per day or more by dermal contact (Union Carbide, 1980).

2.4.3.4 Subchronic toxicity[4]

2.4.3.4.1 Oral

In the only subchronic oral study in rats identified (NTP, 1993), regenerative hemolytic anemia, characterized by decreases in red blood cell count, hemoglobin concentration and hematocrit and increases in mean cell volume, mean cell hemoglobin and reticulocyte count, was observed following exposure to 2-butoxyethanol in the drinking water for 13 weeks. Female F344/N rats were more sensitive than males to 2-butoxyethanol-induced hematological effects, as alterations in most of these parameters were observed in all dose groups (i.e., ≥750 mg/L in drinking water, or ≥82 mg/kg-bw per day) in females and only in the higher dose groups (i.e., ≥1500 mg/L or ≥129 mg/kg-bw per day) in males. Relative weights of several organs were increased, with females again being more sensitive than males. Histopathological changes were observed in the liver, spleen, bone marrow and uterus, with effects (cytoplasmic alteration, possibly associated with enzyme induction) being observed in the liver at all doses in both sexes. The LOEL for hematological and hepatic effects was considered to be 750 mg/L, or 69 and 82 mg/kg-bw per day in males and females, respectively.

Hematological parameters were not examined in the two identified subchronic oral studies in mice (Heindel *et al*., 1990; NTP, 1993). The most sensitive effect observed in B6C3F$_1$ mice administered 2-butoxyethanol in the drinking water for 13 weeks was increased relative kidney weight in female mice at all exposure levels (i.e., ≥750 mg/L or ≥185 mg/kg-bw per day); there were no accompanying histopathological changes in the kidney (NTP, 1993). Altered organ weights (kidney and liver), along with decreased body weights, were also observed in CD-1 mice exposed to a concentration of 2-butoxyethanol in drinking water equivalent to a dose of 1300 mg/kg-bw per day for 15 weeks, although no histopathological changes were noted. These effects were not noted at the lower dose of 700 mg/kg-bw per day (Heindel *et al*., 1990).

2.4.3.4.2 Inhalation

Based on results of a subchronic inhalation study in F344/N rats exposed to up to 500 ppm (2415 mg/m^3) for 14 weeks (NTP, 1998), there were changes in hematological parameters characteristic of macrocytic, normochromic, responsive anemia (i.e., increased mean cell volume, lack of change in mean cell hemoglobin values and increased reticulocyte count). Females were more sensitive than males, with alterations in hematological parameters observed at the lowest concentration tested (i.e., LOEL of 31 ppm [150 mg/m^3]) in females, while the LOEL in males for these effects was 125 ppm (604 mg/m^3); the NOEL in males was considered to be 62.5 ppm (302 mg/m^3). The severity of these effects increased with concentration in both sexes, and there was no evidence of amelioration in response over time. In addition, in female rats at the higher concentrations there was an increased incidence of thrombosis in the blood vessels of several tissues as well as bone infarction, which was hypothesized to have resulted from severe acute hemolysis or anoxic damage to endothelial cells, causing compromised blood flow. Other effects consistent with regenerative anemia observed in both male and female rats included excessive hematopoietic cell proliferation in the spleen, hemosiderin pigmentation in the hepatic Kupffer cells and renal cortical tubules and bone marrow hyperplasia. Inflammation and/or hyperplasia of the forestomach also occurred in rats of both sexes exposed to the higher concentrations (250 and 500 ppm [1208 and 2415 mg/m^3]), while changes in relative kidney and liver weights were noted at 62.5 ppm (302 mg/m^3) and above in females and 250 ppm (1208 mg/m^3) and above in males.

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[4] In this section, effect levels are presented as Lowest-Observed-Effect Levels (LOELs) or NOELs; for discussion of the biological significance of the observed effects, see Section 3.3.3.1.

Hematological effects, consisting of slight changes in red blood cell count, hemoglobin levels and mean corpuscular hemoglobin, were also observed in female Fischer 344 rats exposed to 77 ppm (372 mg/m^3) for 6 weeks (Dodd *et al.*, 1983); however, after 13 weeks of exposure, values for these parameters were generally similar to those of controls (contrary to the observations in this strain of rats by the NTP [1998]). Males appeared to be much less sensitive, as the only effect on blood was a very slight decrease in red blood cell count after 13 weeks at 77 ppm (372 mg/m^3). No indication of hematotoxicity was observed at 25 ppm (121 mg/m^3), which is considered to be the NOEL. No histopathological changes or alterations in clinical chemistry were noted in exposed rats (Dodd *et al.*, 1983). Conversely, however, renal tubular nephritis was reported in Wistar rats (primarily in males) exposed to 100 ppm 2-butoxyethyl acetate (654 mg/m^3, equivalent to 484 mg 2-butoxyethanol/m^3) for 10 months, although there were no hematological effects (based on a limited range of parameters) (Truhaut *et al.*, 1979).

Alterations in hematological parameters indicative of hemolytic anemia (hemoglobin, hematocrit and erythrocyte counts) were also the most sensitive endpoints observed in B6C3F$_1$ mice exposed for 13 weeks (NTP, 1998). However, the anemia in mice was considered to be normocytic, normochromic and responsive (compared to the macrocytic anemia noted in rats), as 2-butoxyethanol did not induce any changes in mean cell volume. In addition, based on the magnitude of the changes, the anemia was less severe in mice than in rats, although females were again more sensitive than males (LOELs in females and males of 31 ppm [150 mg/m^3] and 125 ppm [604 mg/m^3], respectively). As in rats, effects consistent with regenerative anemia (hemosiderin pigmentation and increased hematopoiesis in the spleen) were also observed. The incidence of hyperplasia of the forestomach was increased in female mice exposed to 125 ppm (604 mg/m^3) or more and in males at the highest concentration, 500 ppm (2415 mg/m^3); various lesions also appeared in other tissues in females at 500 ppm (2415 mg/m^3) (a concentration that was also associated with increased mortality in both sexes).

Increased osmotic fragility of erythrocytes, transient hemoglobinuria and reversible changes in liver weights were observed in C3H mice following exposure to concentrations of 2-butoxyethanol of 100 ppm (483 mg/m^3) or more for up to 90 days; however, erythrocytes returned to normal between exposure episodes (Carpenter *et al.*, 1956).

Similar to the results reported for rats in the same study, renal tubular nephritis was observed in rabbits exposed to 100 ppm 2-butoxyethyl acetate (654 mg/m^3, equivalent to 484 mg 2-butoxyethanol/m^3) for 10 months, although there were no effects on hematological or urinalysis parameters (Truhaut *et al.*, 1979).

2.4.3.4.3 Dermal

No overt signs of toxicity and no effects on the weight or microscopic appearance of unspecified organs or on hematology (including osmotic fragility tests) were observed in rabbits administered daily dermal applications (covered) of up to 150 mg 2-butoxyethanol/kg-bw per day for 13 weeks (CMA, 1983).

2.4.3.5 Chronic toxicity and carcinogenicity[5]

Results are available for 2-year bioassays in rats and mice (NTP, 1998). Similar to the critical endpoints observed in shorter-term studies, chronic exposure to 31.2 ppm (151 mg/m^3, the lowest concentration tested) 2-butoxyethanol or greater resulted in hemolytic anemia (characterized as macrocytic, normochromic anemia based on decreases in hematocrit, hemoglobin concentrations and erythrocyte counts, increases in mean cell volume and mean cell hemoglobin, and the lack of effect on mean cell hemoglobin concentration) in F344/N rats. Consistent with results observed in earlier studies and toxicokinetic data that indicate slower clearance of the active metabolite, BAA, and greater activity of the relevant isoenzyme in females (see Section 2.4.3.11), in general, the severity of hematological effects was greater in females than in males, with alterations in multiple parameters being observed at the lowest concentration tested (i.e., 31.2 ppm [151 mg/m^3], considered to be the LOEL), while only mean cell volume was affected in males at this concentration. The severity of these effects increased with exposure level and were persistent throughout the 12 months during which hematological parameters were monitored; there was no indication of amelioration over time in males, while in females, there were slight decreases in the magnitude of the changes in some parameters at 12 months. The anemia was considered to be responsive, based on the observation of increased reticulocyte and nucleated erythrocyte counts and a decrease in the myeloid to erythroid ratios.

There was a marginal increase in the incidence of pheochromocytomas (primarily benign, with one case of malignant tumour) of the adrenal gland in female rats at the highest concentration (125 ppm [604 mg/m^3]), which, while not significantly elevated compared with concurrent controls, was greater than the incidence of this lesion observed in historical controls at the National Toxicology Program (NTP). There was also a non-statistically significant increase in the incidence of hyperplasia of the adrenal medulla of females at 125 ppm (604 mg/m^3). No such increases were observed in males. Other exposure-related histopathological changes observed in rats included increased incidences of minimal hyaline degeneration of the olfactory epithelium (which was considered to be adaptive/protective rather than adverse), increased incidences of Kupffer cell pigmentation in the liver of both sexes at the two highest concentrations, and an increase in splenic fibrosis in males at 62.5 ppm (302 mg/m^3) and above. Based on the results of this study, the NTP concluded that there was no evidence of carcinogenic activity in male F344/N rats and equivocal evidence of carcinogenic activity in female rats of this strain, since the slight increase in pheochromocytomas could not be attributed with certainty to exposure to 2-butoxyethanol.

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[5] In this section, effect levels are presented as LOELs or NOELs; for discussion of the biological significance of the observed effects, see Section 3.3.3.1.

Consistent with the results reported for shorter-term studies, B6C3F$_1$ mice were less sensitive than rats to the hematological effects associated with exposure to 2-butoxyethanol. Anemia, characterized by decreases in hematocrit, hemoglobin concentrations and erythrocyte count, was present in mice exposed to the two higher concentrations (125 and 250 ppm [604 and 1208 mg/m^3]), and there was some evidence of anemia in females at 62.5 ppm (302 mg/m^3), but only at one time point. In general, based on the lack of consistent changes in mean cell volume and mean cell hemoglobin concentrations, the effects were consistent with normocytic, normochromic anemia. Although considered responsive, based on the increased reticulocyte counts, this response ameliorated over time. In addition, contrary to the observations in rats, there were no decreases in myeloid to erythroid ratios; in fact, there were increases in some exposed groups. Thrombocytosis was present in both sexes of mice at all concentrations, based on the increase in platelet counts, with time of appearance being inversely related to concentration. As in rats, females were more sensitive than males, with significant alterations in hematological parameters generally occurring earlier and at lower exposure levels in female mice.

Although less sensitive than rats to the hematotoxicity of 2-butoxyethanol, several other non-neoplastic and neoplastic effects occurred at lower concentrations in mice than in rats following chronic exposure. There were increased incidences of papillomas or carcinomas (combined) of the forestomach in both sexes, which were statistically significant in females exposed to 250 ppm (1208 mg/m^3) compared with concurrent and historical controls and in males at 125 and 250 ppm (604 and 1208 mg/m^3) compared with historical controls (but not study controls). In addition, the incidence of hyperplasia of the epithelium of the forestomach was significantly increased in a concentration-related manner in all exposed groups, which was accompanied by a concentration-related trend in the incidence of ulcers of the forestomach in female mice. The severity of the epithelial hyperplasia in females also increased with exposure level, as mean severity scores in animals with lesions were 1.8, 2.0, 2.4 and 2.9 at 0, 62.5, 125 and 250 ppm (0, 302, 604 and 1208 mg/m^3), respectively.

There was also a concentration-related increase in the incidence of hemangiosarcomas of the liver in male mice (significant at 250 ppm [1208 mg/m^3]); hemangiosarcomas were also detected in the bone marrow of two mice exposed to 250 ppm (1208 mg/m^3) (one of which also had a hemangiosarcoma in the spleen, while the other had a hemangiosarcoma in the heart) and in one mouse exposed to 62.5 ppm (302 mg/m^3). A significant increase in the incidence of hepatocellular carcinomas was also observed in males at the highest concentration, although the incidence was within the range observed in historical controls. In addition, the incidences of hepatocellular adenomas were lower in exposed mice than in controls, and there was no indication of an association between exposure and induction of a related preneoplastic lesion. In spite of these facts, a potential role of 2-butoxyethanol in the development of malignant liver tumours could not be ruled out, and it was concluded that they may be exposure-related. Hemosiderin pigmentation of the Kupffer cells of minimal severity was also noted in the liver of exposed mice, which did not appear to be directly correlated to the incidence of neoplastic lesions in this organ.

Based on the increased incidence of hemangiosarcoma of the liver (males) and squamous cell papillomas or carcinomas of the forestomach (females), it was concluded that there was some evidence of carcinogenic activity of 2-butoxyethanol in male and female B6C3F$_1$ mice, and the Lowest-Observed-Adverse-Effect Level (LOAEL) for non-neoplastic effects (hematotoxicity and forestomach lesions) was 62.5 ppm (302 mg/m^3) in both sexes.

2.4.3.6 Genotoxicity

The results of available *in vitro* genotoxicity assays in mammalian cell lines have been somewhat mixed. Overall, there is equivocal evidence that 2-butoxyethanol may be very weakly genotoxic *in vitro*, as it was mutagenic at the *hprt* locus in Chinese hamster lung cells (Elias *et al*., 1996), but not at the *hprt* or *gpt* locus in Chinese hamster ovary cells (Union Carbide, 1989; Chiewchanwit and Au, 1995), and weakly positive or equivocal results were obtained for unscheduled DNA synthesis, micronuclei and mitotic division aberrations/aneuploidy (Union Carbide, 1989; Elias *et al*., 1996). Results for chromosomal aberrations were negative, while those for sister chromatid exchange were mixed (Union Carbide, 1989; Villalobos-Pietrini *et al*., 1989; NTP, 1993, 1998; Elias *et al*., 1996). 2-Butoxyethanol induced cell transformation at high concentrations and also inhibited intercellular communication (Welsch and Stedman, 1984; Kerckaert *et al*., 1996). However, it is important to note in interpretation of these data that exogenous metabolic activation was incorporated in few of these studies, particularly since the metabolites of 2-butoxyethanol, butoxyacetaldehyde and BAA, were genotoxic in mammalian cells *in vitro* (Elias *et al*., 1996), with the intermediate butoxyacetaldehyde being significantly more active than the principal metabolite, BAA. Neither 2-butoxyethanol nor its metabolites induced mutations in prokaryotes (Kvelland, 1988; Zeiger *et al*., 1992; NTP, 1993, 1998; Hoflack *et al*., 1995; Gollapudi *et al*., 1996).

In the few *in vivo* studies identified, 2-butoxyethanol did not induce micronuclei in the bone marrow of mice or rats administered up to 1000 mg/kg-bw via intraperitoneal injection (Elias *et al*., 1996; NTP, 1998) (which is significant in that the hematopoietic system has been demonstrated to be a target of 2-butoxyethanol-induced effects at much lower doses via ingestion and inhalation, some of which might be secondary to toxicity to circulating blood cells), nor were DNA adducts observed in several tissues examined in rats or transgenic mice exposed to 120 mg/kg-bw as a single oral dose or via repeated subcutaneous administration (Keith *et al*., 1996). Available *in vivo* data for the metabolites are limited to a single study in which BAA also did not induce micronuclei in the bone marrow of mice (Elias *et al*., 1996).

2.4.3.7 Developmental and reproductive toxicity

In the available studies involving oral, inhalation or dermal exposure of Fischer 344 or Sprague-Dawley rats, CD-1 mice or New Zealand white rabbits, embryotoxic or fetotoxic effects or malformations have generally been observed only at or above doses that were also maternally toxic (Hardin *et al.*, 1984; Schuler *et al.*, 1984; Wier *et al.*, 1987; NTP, 1989; Heindel *et al.*, 1990). Hematological effects were reported in the fetuses of Fischer 344 rats exposed to 300 mg/kg-bw per day (which was also hematotoxic in the dams) (NTP, 1989), suggesting that the blood is also a sensitive target tissue in the developing young following *in utero* exposure. Although a slight decrease in live pup weight was reported in CD-1 mice exposed to 700 mg/kg-bw per day in the drinking water, no statistically significant effects on pup weight were observed in the second generation exposed to the same dose (Heindel *et al.*, 1990).

In the only study on the effects of exposure to 2-butoxyethanol on reproductive ability, fertility in female CD-1 mice (based on litter size and the proportion of live pups) was significantly reduced following administration of 1% 2-butoxyethanol or more in the drinking water (1300 mg/kg-bw per day), although these doses were also associated with high mortality (Heindel *et al.*, 1990). (It has been hypothesized that fetal deaths may have been due to hydrops foetalis, associated with severe anemia induced by 2-butoxyethanol or its metabolite, BAA, transported across the placenta [Atkins, 1999]; however, no description of the possible cause of fetal death was presented in the report of this study.) Effects on male and female reproductive organs (including reduced weight or histopathological changes in the epididymis or testes, decreased sperm concentration, altered sperm morphology or uterine atrophy) were noted in F344 rats and $B6C3F_1$ mice exposed to 2-butoxyethanol in the subchronic studies conducted by the NTP (1993, 1998), although some of these effects were not considered to be of biological significance and occurred only at doses or concentrations that also induced hematological and other effects. No effects on the testes were observed in acute or short-term studies (Nagano *et al.*, 1979, 1984; Doe, 1984; Grant *et al.*, 1985; Krasavage, 1986; Exon *et al.*, 1991).

2.4.3.8 Immunotoxicity

Based on the limited available data, 2-butoxyethanol appears to have some immunomodulating potential, with mice being more sensitive than rats. Significant effects on indicators of immune function were observed in BALB/c mice administered repeated oral doses of 50 mg/kg-bw per day or more (Morris *et al.*, 1996), while only slight or no changes in immune function parameters were noted in Fischer 344 and Sprague-Dawley rats administered higher doses (Exon *et al.*, 1991; Smialowicz *et al.*, 1992). Repeated dermal application of 1500 mg 2-butoxyethanol/kg-bw per day also resulted in reduced immune response in BALB/c mice (Singh *et al.*, 1998); no similar studies in rats were identified. Reduced weights or histopathological changes were observed in the thymus or spleen of both mice and rats exposed subchronically or chronically to 2-butoxyethanol; however, these effects were considered likely to be secondary to hemolysis and decreased body weight (NTP, 1993, 1998).

2.4.3.9 Neurotoxicity

No investigations of the neurological effects of 2-butoxyethanol have been identified, although various signs of effects on the central nervous system, including loss of coordination, sluggishness, narcosis, muscular flaccidity and ataxia, have been reported at high doses or concentrations in numerous short-term studies (Carpenter *et al.*, 1956; Dodd *et al.*, 1983; Hardin *et al.*, 1984; Krasavage, 1986).

2.4.3.10 Investigations of hemolysis in *in vitro* systems

Differences in species sensitivity to hemolysis induced by 2-butoxyethanol and its metabolites have been investigated in several *in vitro* studies. These data support the hypothesis that BAA is the active metabolite, as it was much more potent than either the parent compound or the acetaldehyde metabolite (Bartnik *et al.*, 1987; Ghanayem, 1989; Sivarao and Mehendale, 1995). Although slight species differences were observed in erythrocytes exposed to 2-butoxyethanol (with humans being less sensitive than rats, mice, dogs and guinea pigs) (Carpenter *et al.*, 1956; Bartnik *et al.*, 1987), variability between species was much more pronounced when cells were exposed to BAA (Bartnik *et al.*, 1987; Ghanayem and Sullivan, 1993; Udden and Patton, 1994), with erythrocytes from humans being less sensitive than those of rats, as well as those from mice and other species.

In Bartnik *et al.* (1987), hemolysis in blood from four adult male Wistar rats and human erythrocytes isolated from the blood of healthy adult male donors (no further details provided) was examined *in vitro*. The lowest concentration of BAA administered (1.25 mM) resulted in 25% hemolysis of rat erythrocytes after 180 minutes. In contrast, 15 mM BAA did not produce measurable hemolysis in human erythrocytes over the same time. In consequence, these data suggest that rat erythrocytes are at least 12 times more sensitive than the human erythrocytes. This study was conducted in washed erythrocytes rather than whole blood, indicating that the species difference in sensitivity *in vitro* must be due to an inherent difference in the erythrocytes, rather than in the extent of plasma protein binding of BAA.

In Ghanayem (1989), pooled erythrocytes from 9- to 13-week-old male F344 rats and erythrocytes from healthy human volunteers (men and women 18–40 years old; n = 3) were similarly exposed to the acetic acid metabolite. At the end of the incubation period (0.25–4 hours), hematocrit and free plasma hemoglobin levels were determined as indicators of swelling of the erythrocytes and hemolysis, respectively. Comparison of the *in vitro* incubation data at 4 hours for rat blood (Table 1) and human blood (Table 2) suggests that the effect of 8.0 mM BAA in humans was less than that of 0.5 mM BAA in rats. Hence, humans may be at least 16 times less sensitive to the effects of BAA than rats, although information from this study is inadequate to define the exact magnitude of the species difference. It is also not clear from the data presented whether the slight changes with human erythrocytes were produced in relation to the initial control value or were compared with data for a 4-hour incubation in the absence of BAA.

Udden (1994) confirmed the lack of hemolysis in human red blood cells incubated with 2 mM BAA in groups of different human subjects, including nine healthy young adults (31–56 years old), nine older subjects (64–79 years old), seven patients with sickle cell disease and three patients with spherocytosis. Despite differences between these groups in the extent of the spontaneous hemolysis on incubation for 4 hours in the absence of BAA, in none of the groups were there significant increases in hemolysis in the presence of 2 mM BAA. These data provide some reassurance that 2 mM BAA is a true "no-effect" concentration in humans, although concentration–response was not examined.

An additional investigation of Udden and Patton (1994) confirms the greater sensitivity of rat erythrocytes compared with human erythrocytes to the acetic acid metabolite of 2-butoxyethanol *in vitro*. The maximum concentration (2 mM) did not produce any detectable effect in human erythrocytes, although it induced rapid hemolysis in rat erythrocytes. Exposure of rat erythrocytes to 0.2 mM BAA did not result in hemolysis, although reduced cell deformability and increased mean cell volume were noted. No details were given of the human subjects who donated erythrocytes.

Comparison of the data of Udden (1994) with those of Udden and Patton (1994), acquired by directly comparable protocols, indicates that the no-effect concentration for hemolysis is 2 mM BAA in human erythrocytes and 0.2 mM in rat erythrocytes. Although very few concentrations were studied, these data support at least a 10-fold difference in sensitivity between rats and humans.

2.4.3.11 Mode of action for hematological effects

2.4.3.11.1 Toxicokinetics

There are species- and sex-related variations in hematological response to 2-butoxyethanol, with rats being the most sensitive species tested to date and that for which most data are available. Effects on the blood have been observed in rats following acute, short-term and long-term exposure by various routes. Hematological effects have been observed in other experimental species; although the database is more limited, in general, effects are induced only at higher exposure levels than those that cause hematotoxicity in rats or occurred at a lesser degree of severity than in rats. For example, while alterations in hematological parameters were observed in subchronic and chronic inhalation studies in both rats and mice (NTP, 1998), the changes in mice were consistent with normocytic anemia, compared with the macrocytic anemia observed in rats.

In both short-term and long-term studies in rats, females have consistently been more sensitive to 2-butoxyethanol-induced hemolysis than males. Although not as dramatic as the sex difference in rats, female mice are also somewhat more sensitive than male mice to the hematotoxicity induced by 2-

butoxyethanol in both the subchronic and chronic studies, with effects generally occurring earlier and at lower concentrations.

These observed species- and sex-related variations in toxicity are well correlated with differences in production and clearance of the acetic acid metabolite of 2-butoxyethanol. Mice appear to clear BAA from the blood at a much greater rate than do rats, with the rate of elimination decreasing with increased duration of exposure to a greater degree in rats than in mice (Dill *et al.*, 1998). Likewise, clearance of BAA from the blood is slower in female rats than in males (Dill *et al.*, 1998); in addition, the activity of hepatic alcohol dehydrogenase enzyme, which is involved in the metabolism of 2-butoxyethanol to BAA, is greater in females than in males (Aasmoe *et al.*, 1998). Ghanayem *et al.* (1987) also observed older rats to be more susceptible to the hemolytic effects of acute 2-butoxyethanol exposure, which is consistent with the greater rate of elimination of metabolites in the urine of younger rats. These observations and additional studies in which oxidation of 2-butoxyethanol to BAA is inhibited indicate that the acid metabolite is principally responsible for the hematological effects observed in experimental animals exposed to the compound.

The specific mode of action by which 2-butoxyethanol induces hematological effects has not been established. Induced changes are those consistent with hemolytic anemia, hemoglobinuria or increased osmotic fragility of erythrocytes. Based on their progression, which includes erythrocyte swelling, morphological changes and decreased deformability (Udden, 1996), effects are likely due to conjugation with the lipids in the membrane of erythrocytes and resulting increases in permeability to cations and water (Ghanayem, 1996).

There are two published physiologically based pharmacokinetic (PBPK) models for 2-butoxyethanol for which metabolism is included, namely those of Corley *et al.* (1994) and Lee *et al.* (1998). For both models, simulated levels of 2-butoxyethanol and BAA in human blood, as well as concentrations of BAA in the urine, fit reasonably well with the data published by Johanson (1986, 1988) and Johanson and Johnsson (1991).

In Corley *et al.* (1994), compartments included lung, rapidly and slowly perfused tissues, fat, skin, muscle, gastrointestinal tract and liver for both 2-butoxyethanol and BAA; the kidney was also added to the BAA description. Partition coefficients were determined experimentally for both 2-butoxyethanol and BAA. Rate constants either were taken from the literature (V_{max} for 2-butoxyethanol to BAA) or were estimated by fitting simulations to experimental data (V_{max} for 2-butoxyethanol to other metabolites and renal elimination constants for BAA). In the absence of data, constants for binding to blood protein for BAA were set to improve the fit of the model. The model reasonably simulated data from studies in young and old male rats exposed intravenously for both 2-butoxyethanol and BAA, with no adjustment of any parameters. Fits of simulations in the case of older rats were improved slightly by increasing the volume of the fat compartment and by decreasing the renal elimination rate, both of which were rationalized as having a biological basis (i.e., these are common changes in aging rats).

The model also gave reasonable predictions of urinary BAA levels, especially at doses below those demonstrated to cause hemolysis. The model predicted uptake and metabolism of 2-butoxyethanol and elimination of BAA in an inhalation experiment in male rats except at the highest concentration, where the amount of BAA excreted was overpredicted. This was possibly due to toxicity as manifested by hemolysis.

Lee *et al.* (1998) designed a model to describe the toxicokinetics of 2-butoxyethanol and BAA in different species following repeated long-term exposures (based on the data from studies conducted in rats and mice by the NTP; Dill *et al.*, 1998), and which was developed for the most part using 2-week exposures of male rats to 2-butoxyethanol. Adjustments were made to account for differences in female rats, and then further adjustments were made to better simulate data in mice. The model was subsequently expanded to account for age-related differences likely to be evident in the chronic studies used to develop the model.

Structural differences in the Lee *et al.* (1998) model include separate kidney and spleen compartments and the inclusion of the muscle in the slowly perfused tissue compartment. Tissue to blood partition coefficients were the same as those in the Corley *et al.* (1994) model, and organ weights as percentages of body weight were very similar in the two models, with the exception of those for liver and lung.

These models do not incorporate results of recent *in vitro* investigations, in which hepatocytes from rats metabolized 2-butoxyethanol to BAA more efficiently than cells from humans; this pathway was also saturated at much lower doses in human hepatocytes (Green *et al.*, 1996).

2.4.3.11.2 Toxicodynamics

Results of *in vitro* investigations of the comparative sensitivity of erythrocytes from several mammalian species (including humans) to hemolysis induced by 2-butoxyethanol or BAA indicated that cells from humans were less sensitive than those from rats (the most sensitive species *in vivo*), mice, dogs, guinea pigs, hamsters and baboons (Carpenter *et al.*, 1956; Bartnik *et al.*, 1987; Ghanayem and Sullivan, 1993; Udden and Patton, 1994), as discussed in Section 2.4.3.10.

2.4.4 Humans

Alterations in various hematological parameters were noted in several case reports involving incidental exposure to 2-butoxyethanol (Rambourg-Schepens *et al.*, 1988; Gijsenbergh *et al.*, 1989; Bauer *et al.*, 1992), but not in a survey of childhood poisonings by oral doses estimated to be as high as 1850 mg/kg-bw (Dean and Krenzelok, 1992). In a recent cross-sectional survey, slight, but statistically significant, changes in some hematological parameters (hematocrit and mean corpuscular hemoglobin concentration) were observed in a group of 31 men occupationally exposed to average concentrations of 2-butoxyethanol of 3.64 or 2.20 mg/m^3 (based on limited exposure data) compared with unexposed workers (Haufroid *et al*., 1997). However, in the only relevant clinical study identified, no changes in erythrocyte fragility were noted in a small number of men and women (n = 2–4) exposed to up to 195 ppm (942 mg/m^3) for several hours (Carpenter *et al*., 1956).

Other effects characteristic of poisoning with ethylene glycol (a metabolite of 2-butoxyethanol in humans), such as coma, metabolic acidosis and renal effects, as well as changes in levels of hepatic enzymes (of uncertain biological significance) have been reported in several cases or cross-sectional studies (e.g., Rambourg-Schepens *et al*., 1988; Collinot *et al*., 1996; Haufroid *et al*., 1997; Nisse *et al*., 1998).

3.0 PROPOSED ASSESSMENT OF "TOXIC" UNDER CEPA 1999

3.1 CEPA 1999 64(a): Environment

The environmental risk assessment of a PSL substance is based on the procedures outlined in Environment Canada (1997a). Analysis of exposure pathways and subsequent identification of sensitive receptors are used to select environmental assessment endpoints (e.g., adverse reproductive effects on sensitive fish species in a community). For each endpoint, a conservative Estimated Exposure Value (EEV) is selected and an Estimated No-Effects Value (ENEV) is determined by dividing a Critical Toxicity Value (CTV) by an application factor. A conservative (or hyperconservative) quotient (EEV/ENEV) is calculated for each of the assessment endpoints in order to determine whether there is potential ecological risk in Canada. If these quotients are less than one, it can be concluded that the substance poses no significant risk to the environment, and the risk assessment is completed. If, however, the quotient is greater than one for a particular assessment endpoint, then the risk assessment for that endpoint proceeds to an analysis where more realistic assumptions are used and the probability and magnitude of effects are considered. This latter approach involves a more thorough consideration of sources of variability and uncertainty in the risk analysis.

3.1.1 Assessment endpoints

In Canada, most environmental releases of 2-butoxyethanol are to the atmosphere. Based on its predicted environmental partitioning, assessment endpoints for 2-butoxyethanol relate to terrestrial biota, pelagic organisms and soil organisms.

3.1.2 Environmental risk assessment

3.1.2.1 Terrestrial organisms

3.1.2.1.1 Wildlife

For a conservative risk characterization for terrestrial biota, the EEV is 243 $\mu g/m^3$, the highest concentration of 2-butoxyethanol in outdoor air reported in a Canadian multimedia study. This value is believed to be conservative, because the highest concentration of 2-butoxyethanol in the atmosphere in the vicinity of an automotive plant at Windsor, Ontario, was 7.3 $\mu g/m^3$. The estimated concentration of 2-butoxyethanol in Canadian air using ChemCAN modelling based on reported releases in 1996 is several orders of magnitude smaller, 1.267 ng/m^3. Releases of 2-butoxyethanol occurred in three provinces, but, for modelling purposes, it was assumed that all releases occurred in southern Ontario.

The CTV is 31 ppm (150 mg/m^3), the concentration that caused hemolytic anemia in rats and mice. Dividing this CTV by a factor of 10 (to account for the extrapolation from laboratory to field conditions and interspecies and intraspecies variations in sensitivity) gives an ENEV of 3.1 ppm (15 mg/m^3, or 15 000 µg/m^3).

The conservative quotient can be derived as follows:

$$\text{Quotient} = \frac{\text{EEV}}{\text{ENEV}} = \frac{243\ \mu\text{g/m}^3}{15\ 000\ \mu\text{g/m}^3} = 1.6 \times 10^{-2}$$

Therefore, concentrations of 2-butoxyethanol in air appear to be unlikely to cause adverse effects on populations of terrestrial biota.

3.1.2.1.2 Soil organisms

For a conservative risk characterization for soil organisms, the EEV is 3.34 × 10^{-3} ng/g, the estimated concentration of 2-butoxyethanol in soil using ChemCAN modelling, based on reported releases in 1996. This value is believed to be conservative, because releases of 2-butoxyethanol occurred in three provinces, but, for modelling purposes, it was assumed that all releases occurred in southern Ontario.

No information was identified regarding the toxicity of 2-butoxyethanol to soil organisms. Van Leeuwen *et al*. (1992) used quantitative structure–activity relationships to estimate that a sediment concentration of 4600 ng 2-butoxyethanol/g would be hazardous to 5% of benthic species. Using this sediment HC_5 value as a CTV and an application factor of 100 (to account for interspecies and intraspecies variations in sensitivity) gives an ENEV of 46 ng/g for soil organisms.

The conservative quotient is calculated as follows:

$$\text{Quotient} = \frac{\text{EEV}}{\text{ENEV}} = \frac{3.34 \times 10^{-3}\ \text{ng/g}}{46\ \text{ng/g}} = 7.3 \times 10^{-5}$$

Therefore, concentrations of 2-butoxyethanol in soil in Canada are unlikely to cause adverse effects on populations of soil organisms.

3.1.2.2 Aquatic organisms

For a conservative risk characterization for pelagic organisms, the EEV is 2.36×10^{-4} µg/L, the estimated concentration of 2-butoxyethanol in water using ChemCAN modelling, based on reported releases in 1996. This value is believed to be conservative, because releases of 2-butoxyethanol occurred in three provinces, but, for modelling purposes, it was assumed that all releases occurred in southern Ontario.

The CTV for pelagic organisms is 5.4×10^{3} µg/L, the 96-hour LC_{50} for *Palaemonetes pugio*. Dividing this CTV by a factor of 100 (to account for the conversion of an acute LC_{50} to a long-term no-effects value, extrapolation from laboratory to field conditions, and interspecies and intraspecies variations in sensitivity) gives an ENEV of 54 µg/L.

The conservative quotient can be derived as follows:

$$\begin{aligned} \text{Quotient} &= \frac{\text{EEV}}{\text{ENEV}} \\ &= \frac{2.36 \times 10^{-4}\ \mu\text{g/L}}{54\ \mu\text{g/L}} \\ &= 4.4 \times 10^{-6} \end{aligned}$$

Therefore, 2-butoxyethanol concentrations in water in Canada appear to be unlikely to cause adverse effects on populations of pelagic organisms.

In their responses to the CEPA Section 16 survey, two facilities reported releases of 2-butoxyethanol in liquid effluents to water bodies, but details of these releases are considered to be confidential business information. The effluents are treated before release and are considerably diluted in the receiving waters, where further biodegradation would occur. Concentrations of 2-butoxyethanol in the receiving waters would not likely be high enough to affect aquatic organisms.

3.1.2.3 Discussion of uncertainty

There are several sources of uncertainty in this environmental risk assessment. Data about environmental releases in Canada are limited because the substance was not included on the National Pollutant Release Inventory until 1999. Few data were identified on environmental concentrations of 2-butoxyethanol in Canada or in other countries. The EEV for 2-butoxyethanol in air, 243 µg/m^3, is believed to be conservative, as the atmospheric concentration of the substance in the vicinity of an automotive plant in Windsor, Ontario, was only 7.3 µg/m^3. In view of the lack of monitoring data, the

ChemCAN v. 4.0 model was used to estimate environmental concentrations of 2-butoxyethanol in the other environmental compartments (i.e., soil and water), based on the highest reported recent release of the substance in Canada, which occurred in 1996. To make a conservative estimate of environmental concentrations of 2-butoxyethanol, it was assumed, for modelling purposes, that all of this was released into southern Ontario. Kane (1993) compared measured environmental concentrations of five industrial chemicals and six pesticides with environmental concentrations estimated for the substances by the ChemCAN model. Sixty percent of the measured environmental concentrations were within one order of magnitude of predicted values, and 75% were within two orders of magnitude. The highest concentration of 2-butoxyethanol in 29 samples of Ontario drinking water was 5.0 µg/L, a value one order of magnitude below the ENEV. In the only relevant study identified from other countries, the concentration of 2-butoxyethanol in a polluted river in Japan ranged up to 5.68 mg/L, a value that is approximately the same as the CTV and two orders of magnitude above the ENEV. This study, however, was published in 1981.

No information was identified regarding the toxicity of 2-butoxyethanol to soil organisms or to terrestrial wildlife through atmospheric exposure. An estimation of a hazardous concentration to benthic species was the basis for the assessment of risk to soil organisms. The results of inhalation toxicity studies using laboratory strains of rats and mice were used for the assessment of risk to terrestrial biota. It is not possible to directly relate the results of these tests, changes in blood parameters indicative of hemolytic anemia, to the well-being of wildlife species. It is possible, however, that such changes in the blood could have some effect on the ability of wildlife to obtain food or to escape from predators. To account for these uncertainties, application factors were used in the environmental risk assessment to derive ENEVs.

Conservative risk quotients were small for all environmental assessment endpoints. Therefore, despite the data gaps regarding the environmental concentrations and effects of 2-butoxyethanol on soil organisms and terrestrial wildlife, the data available at this time are considered adequate for drawing a conclusion about the environmental risk of the substance in Canada.

3.2 CEPA 1999 64(b): Environment upon which life depends

2-Butoxyethanol does not deplete stratospheric ozone, and its potential for contributing to climate change is negligible. The potential of 2-butoxyethanol for photochemical ozone (smog) creation is moderate, but the low quantities of 2-butoxyethanol in the atmosphere are unlikely to make its contribution significant relative to that of other smog-forming substances.

3.3 CEPA 1999 64(c): Human health

3.3.1 Estimates of potential exposure in humans

Available data on levels of 2-butoxyethanol in environmental media in Canada upon which estimates of population exposure may be based are limited to air and drinking water. In order to determine the relative contribution of these media to total intake, point estimates of average daily intake (on a body weight basis), based on the limited data on mean concentrations in ambient air, indoor air and drinking water reported in the Canadian multimedia exposure study (Conor Pacific Environmental Technologies Inc., 1998) and reference values for body weight, surface area, inhalation volume and amount of drinking water consumed daily, for six age groups in the general population in Canada are presented in Table 3. Although confidence in the results of the multimedia exposure study is low, due to limitations of the analytical methodology (as described in Section 3.3.5), comparison with estimates of intake in air and water on the basis of fugacity modelling and concentrations in ambient air in Windsor, Ontario (OMEE, 1994), indicates that this approach to estimating population exposure is conservative. Based on these values, average daily intake from these environmental media ranges from 5.4 to 15 µg/kg-bw per day. (Average intake of the 50 participants in the multimedia exposure study was determined to be 7.3 µg/kg-bw per day, based on data collected for personal air, drinking water and beverages.) Of the media considered, inhalation in indoor air represents the principal route of exposure, with outdoor air and dermal absorption of airborne 2-butoxyethanol contributing smaller amounts, and exposure via drinking water being negligible in comparison.

Reasonable worst-case estimates of intake, based on maximum concentrations measured in indoor and outdoor air in the multimedia exposure study (although, again, the limitations of this study are acknowledged), as well as the highest concentration detected in a survey of drinking water in Ontario (OMEE, 1996), for these same six age groups ranged from 91 to 262 µg/kg-bw per day, as presented in Table 4. Again, for the media considered, inhalation in indoor air represented the major route of exposure to 2-butoxyethanol.

Since no monitoring data are available, it is not possible to determine the contribution of food to the overall intake of 2-butoxyethanol. However, 2-butoxyethanol is released primarily to air from industrial activities and through volatilization from consumer products and is unlikely to partition to food from air, based on its very low log K_{ow} (0.84) and low bioconcentration factor. Indeed, based on physical/chemical properties, the principal source of 2-butoxyethanol in food is likely to be water, for which reported concentrations are very low. (The solubility of 2-butoxyethanol is high, and it is predicted to remain in water if released or distributed to that medium.) In addition, if intake in food were estimated on the basis of concentrations predicted in terrestrial animals and plants by fugacity modelling, these values would be more than two orders of magnitude less than the estimated average intake from indoor air for an average adult, based on data from the multimedia exposure study. Exposure to 2-butoxyethanol in soil is likely to be negligible in comparison with that estimated for indoor air, based on its release patterns and the relatively small quantities ingested.

Direct exposure to 2-butoxyethanol can result from the use of a variety of consumer products containing the substance. Concentrations of 2-butoxyethanol in indoor air resulting from the use of consumer products were estimated based on the rates of emission from various products investigated by Health Canada (Cao, 1999) (cleaners, nail polish remover and hair colorant) and are presented in Table 5. Assuming "standard" room conditions and a conservative rate of air exchange, concentrations estimated for these products could range up to 446 mg/m^3 from use of a liquid cleaner. Intake of 2-butoxyethanol via inhalation was also estimated, based on these predicted airborne concentrations, on a per event basis, as well as average daily intakes based on annual event frequencies. Because most of the consumer products are used primarily by adults, estimated exposures have been derived for this age group only. (The differences in intake from a given medium among age classes, as a result of age-specific differences, would be small in relation to the variation in exposure from the various sources, in any case.) Intake per event via inhalation from use of these products, assuming 100% absorption of the inhaled substance, is estimated to range up to 3.8 mg/kg-bw; estimated average daily intake of 2-butoxyethanol from products such as all-purpose or glass cleaners would be similar, due to their frequent use. Concentrations in indoor air resulting from use of cosmetic products, including nail polish remover and hair colorant, are estimated to range up to 25 mg/m^3, with intake potentially being as high as 0.23 mg/kg-bw per event (0.008 mg/kg-bw per day).

Upper-bounding estimates of intake of 2-butoxyethanol were also derived for those few consumer product groups for which data on composition were available (cosmetics, household cleaners, paints and paint thinners), as described in Table 5. These estimates are based on standard product use scenarios and the maximum concentration of 2-butoxyethanol in the products, and they assume 100% transfer of 2-butoxyethanol from the product into air (for inhalation exposure estimates) and 100% absorption of the substance inhaled or contacting the skin (in view of lack of adequate data to support more refined estimates). For some liquid products for which dermal contact is expected, exposure may occur via both inhalation and dermal absorption.

Since these latter estimates do not incorporate measured data on emissions, they are considered less reliable. However, for products similar to those for which exposure was estimated based on data on emissions (nail polish remover and all-purpose liquid cleaners), the less certain estimates based on product composition information were generally in the same range (maximum indoor air concentration of 175 mg/m^3 from all-purpose liquid cleaners, assuming 100% volatilization and no exchange of air, and maximum intake per event of 4.3 mg/kg-bw via dermal absorption from nail polish remover). Upper-bounding estimates of concentrations of 2-butoxyethanol in indoor air resulting from the use of spray cleaner containing the substance range up to 380 mg/m^3 (with intake of up to 3.3 mg/kg-bw per event via inhalation and 1.0 mg/kg-bw per day via dermal absorption).

Upper-bounding estimates of intake of 2-butoxyethanol via inhalation through use of paints containing the substance were high (1855 mg/kg-bw per event or 36 mg/kg-bw per day), while dermal absorption would contribute only 2.3 mg/kg-bw per event (0.04 mg/kg-bw per day). Paint thinners may contribute up to 8.7 mg/kg-bw per event (1.2 mg/kg-bw per day) via dermal absorption and up to 119 mg/kg-bw per event (16 mg/kg-bw per day) via inhalation. Concentrations in indoor air resulting from use of these products could range up to 18 390 mg/m^3. Although emissions from paints or paint thinners were not investigated by Health Canada (Cao, 1999), Norbäck *et al.* (1995, 1996) reported that personal air samples collected in the breathing zone of Swedish house painters using water-based paints under "normal" working conditions contained a mean concentration of 59 mg 2-butoxyethanol/m^3 (maximum 730 mg/m^3).

While these estimates are uncertain and should be considered as upper bounding, particularly those for which 2-butoxyethanol-specific data are restricted to product composition, predicted values for several of the products are supported by more robust estimates based on monitoring of product emissions.

3.3.2 Human health hazard characterization

Few data were identified on the potential effects of 2-butoxyethanol in humans. Although effects on the blood have been observed in exposed workers and in several cases of incidental exposure (Rambourg-Schepens *et al.*, 1988; Gijsenbergh *et al.*, 1989; Bauer *et al.*, 1992; Haufroid *et al.*, 1997), due to limitations of these studies, characterization of health hazards associated with 2-butoxyethanol is based primarily on studies in experimental animals.

3.3.2.1 Hematological effects

The majority of toxicological investigations with 2-butoxyethanol have been conducted in rats, in which the most sensitive target tissue is apparently the blood. Acute exposure to 2-butoxyethanol via oral (Ghanayem *et al.*, 1987), inhalation (Carpenter *et al.*, 1956) or dermal (Bartnik *et al.*, 1987) routes resulted in alterations in hematological parameters characteristic of hemolytic anemia, hemoglobinuria or increased osmotic fragility of erythrocytes. Similar effects were observed in rats following short-term oral or inhalation exposure to 2-butoxyethanol (Carpenter *et al.*, 1956; Dodd *et al.*, 1983; NTP, 1989). In some of these studies, the effects appeared to be reversible after cessation of exposure, as the severity of the hematological changes decreased with increasing time since exposure (Grant *et al.*, 1985; Krasavage, 1986; NTP, 1989; Ghanayem *et al.*, 1992). Similarly, tolerance, or autoprotection, was suggested by the results of two studies in which the hematological effects were less severe in rats that had been exposed to 2-butoxyethanol prior to administration compared with those in rats receiving only the subsequent doses, although the protective effect declined with increasing time between exposures. In addition, bleeding rats prior to acute exposure to 2-butoxyethanol reduced the severity of the hematotoxicity (Ghanayem *et al.*, 1992; Sivarao and Mehendale, 1995). These data suggest that older red blood cells are more susceptible to 2-butoxyethanol-induced effects (which has also been demonstrated in *in vitro* studies); as they are replaced by more resilient younger cells, the severity of the hematotoxic response declines.

However, such reversibility or autoprotection is likely limited, since it was not observed in rats repeatedly exposed to 2-butoxyethanol for longer durations. In rats exposed to 2-butoxyethanol in the drinking water for 13 weeks, symptoms of regenerative hemolytic anemia were still present at the end of the study in females at all doses tested (NTP, 1993). Similar effects were also noted in the same strain of rats exposed via inhalation for 14 weeks to 2-butoxyethanol at all concentrations tested, based on results of studies conducted by the NTP (1998). The anemia was considered to be macrocytic, normochromic and responsive. Other indicators of regenerative anemia, including increased hematopoiesis, hemosiderin accumulation in the liver and kidney and bone marrow hyperplasia, were also observed in both sexes; thrombosis, likely associated with severe acute hemolysis, was also noted in females at the higher exposure levels. In addition, in the chronic study conducted by the NTP (1998), in which rats were exposed to 2-butoxyethanol by inhalation for up to 2 years, hemolytic anemia was evident in animals monitored at regular intervals up to 12 months. The anemia, which was again characterized as macrocytic, normochromic and responsive, was observed at all concentrations; the severity of the effects increased with exposure level and did not ameliorate significantly over time.

2-Butoxyethanol-induced hematological effects have also been observed in other species of experimental animals. In mice, a decrease in red blood cell count was noted following short-term oral exposure (Nagano *et al*., 1979, 1984), while alterations in hematological parameters were reported in subchronic and chronic inhalation studies (NTP, 1998), although, as discussed above, mice appear to be less sensitive to 2-butoxyethanol-induced hematotoxicity than rats. Hematological effects were also noted in limited short-term studies in rabbits, dogs and monkeys (Carpenter *et al*., 1956; Truhaut *et al*., 1979; Union Carbide, 1980; Tyl *et al*., 1984), although available data are inadequate to evaluate differences in species sensitivity. In general, these effects were observed only at doses greater than those that induced similar, more severe effects in rats.

There is also some evidence that the blood is a sensitive target tissue in the developing young following *in utero* exposure to 2-butoxyethanol in both rats and mice. Hematological effects were reported in the fetuses of rats exposed to doses of 2-butoxyethanol that were also hematotoxic in the dams (NTP, 1989), while an increase in fetal mortality in mice (Heindel *et al*., 1990) has been hypothesized to be due to hydrops foetalis, associated with severe anemia induced by 2-butoxyethanol or its metabolite, BAA, transported across the placenta (Atkins, 1999); however, no description of the possible cause of fetal death was presented in the report of this study.

In view of the extensive database that indicates that 2-butoxyethanol is hematotoxic in multiple experimental species, and the limited evidence of changes in hematological parameters in occupationally and incidentally exposed humans, 2-butoxyethanol is considered likely to be hematotoxic in humans. Although limited, available data from toxicokinetic studies and comparative *in vitro* investigations suggest that humans may be less sensitive to 2-butoxyethanol-induced hematotoxicity than rats (although no data were identified on inter-individual sensitivity in humans), which, at least based on the results of *in vivo* studies, appear to be the most sensitive of the animal species investigated.

3.3.2.2 Other non-neoplastic effects

Other target organs of 2-butoxyethanol-induced effects in various species (rats, mice, rabbits or guinea pigs) following acute, short-term or long-term exposure (Carpenter *et al*., 1956; Truhaut *et al*., 1979; Krasavage, 1986; Bartnik *et al*., 1987; Ghanayem *et al*., 1987; NTP, 1993, 1998) include the liver, kidney, spleen and bone marrow. Many of the observed effects, such as accumulation of hemosiderin pigment, increased hematopoiesis and cellularity, and hemoglobinuria, are considered to be secondary or in response to hemolytic anemia (NTP, 1998), while other effects, such as alterations in relative organ weights and some histopathological changes, occurred only at doses that were also hemolytic. Although cytoplasmic changes were noted in the liver of male rats exposed subchronically to oral doses lower than those that induced alterations in blood parameters (although these doses were hematotoxic in females), these effects may have been related to induction of enzymes involved in metabolism of 2-butoxyethanol (NTP, 1993).

The forestomach was also a critical target for 2-butoxyethanol-induced toxicity in mice. In the chronic study in mice, increased incidences of inflammation, epithelial hyperplasia and/or ulceration were noted at all concentrations tested (with females being more sensitive than males) following inhalation, with some evidence of concentration-related trends in incidence and severity of forestomach lesions in female mice; these effects were also observed in both mice and rats subchronically exposed to higher concentrations that also induced hematological changes (NTP, 1998). These effects on the forestomach are also in concordance with neoplastic lesions at this site in mice. While the greater sensitivity of females is consistent with renal clearance of one of the metabolites being limiting, data on effects of the various metabolites of 2-butoxyethanol on the forestomach have not been identified. Effects are similar to those caused by well-studied aldehydes, suggesting that metabolites other than BAA may play a role. Relevant data to assess the relative sensitivity of the forestomach of rodents in comparison with the glandular stomach of humans were not identified.

In investigations of the potential developmental toxicity of 2-butoxyethanol in rats, mice or rabbits, embryotoxic or fetotoxic effects or malformations have generally been observed only at or above doses that are also maternally toxic (Hardin *et al*., 1984; Schuler *et al*., 1984; Wier *et al*., 1987; NTP, 1989; Heindel *et al*., 1990). Similarly, effects on female reproductive ability or on male and female reproductive organs (some of which were not considered to be of biological significance) were observed only at doses or concentrations that were associated with high mortality or that were greater than those that induced hematotoxicity (Heindel *et al*., 1990; NTP, 1993, 1998).

Based on limited data, 2-butoxyethanol does not appear to induce immunological effects at doses lower than those associated with hematotoxicity or other adverse effects (Exon *et al*., 1991; Smialowicz *et al*., 1992). Data on the potential effects of 2-butoxyethanol on the nervous system are insufficient for evaluation.

3.3.2.3 Carcinogenicity and genotoxicity

In the chronic bioassays conducted by the NTP (1998), significantly increased incidences of tumours were observed only at the higher concentrations tested (in some cases only when compared with historical controls), and these incidences were generally only marginally increased. There is some indication that neoplasms at one site (i.e., the forestomach) represent a progression from non-neoplastic effects associated with local inflammation and response. Although the potential relation between these lesions was not investigated, it was ascertained that induction of tumours at this site did not involve mutations of the H-*ras* oncogene (codon 61), based on examination of mutational spectra in tumours of exposed and control mice. While it was concluded that there was some evidence of carcinogenicity in mice (based on increased incidences of hemangiosarcomas of the liver in males and squamous cell papillomas of the forestomach in females), the evidence in female rats was considered only equivocal (based on a marginal increase in the incidence of benign or malignant pheochromocytomas of the adrenal gland). Information on the mode of induction of these tumours was not identified.

The apparent low carcinogenic potency of 2-butoxyethanol is in concordance with equivocal evidence that 2-butoxyethanol may be weakly genotoxic *in vitro*. The observations that 2-butoxyethanol did not induce DNA adducts at several sites in exposed rodents but did induce mitotic division aberrations/aneuploidy (possibly due to interference with spindle formation) and inhibit intercell communication would support the hypothesis that the induction of these tumours may not involve direct interaction of 2-butoxyethanol with genetic material. However, positive or equivocal results were obtained for induction of other endpoints by the parent compound and its metabolites. In addition, 2-butoxyethanol did not promote initiated cells in a transgenic mouse assay (Keith *et al.*, 1996). Therefore, on the basis of limited evidence of carcinogenicity in rodents and genotoxicity in *in vitro* assays, for which the potency appears to be low, 2-butoxyethanol is considered to be possibly weakly carcinogenic in humans.

3.3.3 Exposure–response analyses

Based on available data, inhalation in indoor air is an important route of exposure to 2-butoxyethanol for the general population, particularly for those using consumer products that contain the substance. Since intake in food is highly uncertain (relevant monitoring data have not been identified) but is expected to be low, as levels in water, the likely principal source in food, are low, exposure–response relationships for health effects associated with 2-butoxyethanol have been quantified for the inhalation route only.

As discussed above in Section 3.3.2, effects on the blood appear to be the critical effect most consistently associated with exposure to 2-butoxyethanol, based on data from the limited epidemiological investigations identified as well as acute, short-term and long-term studies in multiple species of animals exposed via inhalation, ingestion or dermal contact. Slight, but statistically significant alterations in hematological parameters were noted in a group of workers exposed to concentrations as low as approximately 2 mg/m^3, although information in this study is inadequate to quantitate exposure–response. In several of the available studies in experimental animals, effects on the blood were reported at the lowest dose or concentration tested, with the lowest reported LOEL for alterations in various parameters being 31.2 ppm (151 mg/m^3) (observed in subchronic and chronic studies in rats). In view of the sufficient weight of evidence for the hematotoxicity of 2-butoxyethanol, therefore, Benchmark Concentrations (BMCs) for a variety of hematological endpoints were derived on the basis of the long-term studies in animals in which adequate exposure–response data were presented.

In addition to alterations in various blood parameters, chronic exposure to 2-butoxyethanol was also associated with increased incidence of hemosiderin pigmentation of the Kupffer cells of the liver in male and female rats and female mice at all concentrations tested (i.e., ≥31.2 ppm [≥151 mg/m^3]) and in male mice at ≥125 ppm (≥604 mg/m^3). Although such accumulation of pigment was considered to be the result of the 2-butoxyethanol-induced hemolytic anemia, these data were used to determine BMCs for a discrete measure of 2-butoxyethanol-induced effects, in addition to the continuous data discussed above for hematological parameters.

Although less consistently observed, the forestomach was also a sensitive target organ in rodents exposed to 2-butoxyethanol via inhalation, with non-neoplastic effects being induced in a chronic study in mice at the lowest concentration investigated (62.5 mg/m^3) and at higher concentrations in a subchronic study in rats (≥250 ppm [≥1208 mg/m^3]). Prolonged exposure to 2-butoxyethanol at concentrations of 250 ppm (1208 mg/m^3) or more was also associated with a significant increase in the incidence of tumours in the forestomach of mice. Therefore, a BMC and a Tumorigenic Concentration were derived for non-neoplastic and neoplastic effects on the forestomach, respectively.

Marginal, but statistically significant, increases in the incidence of other tumours, including hemangiosarcomas of the liver as well as hepatocellular carcinomas, were also observed in male mice at the highest concentration of 2-butoxyethanol (i.e., 250 ppm [1208 mg/m^3]) (NTP, 1998). Therefore, although the weight of evidence for an association with exposure to 2-butoxyethanol is very limited, Tumorigenic Concentrations have been derived for these effects, primarily for comparison with values derived for other endpoints.

Therefore, the principal critical effects for exposure–response analyses for characterization of risk to humans are the hematological effects in rats and mice. Due to the consistency of their observation in a wide range of studies at lowest doses or concentrations, these effects are emphasized. However, lesions in the forestomach of mice are also considered critical, and measures of exposure–response are developed for this endpoint for comparison with estimated exposure. Additional BMCs were also derived for other endpoints, primarily for comparison with those determined for these critical effects.

Based on the available data from short- and long-term studies in various experimental species and *in vitro* investigations in blood cells from animals and humans, as well as information on toxicokinetics and metabolism of 2-butoxyethanol, rats appear to be more sensitive to the hematotoxic effects induced by the substance than other species. Variations in sensitivity to 2-butoxyethanol-induced hematotoxicity are well correlated with variations in production and clearance of BAA. These observations as well as additional studies in which oxidation of 2-butoxyethanol to BAA is inhibited indicate that the acetic acid metabolite is principally responsible for hematological effects associated with 2-butoxyethanol. The major pathways of metabolism and disposition of 2-butoxyethanol are qualitatively similar in rats, mice and humans, with BAA being a major circulating metabolite in all species and being eliminated primarily by renal excretion. However, while there is considerable evidence that BAA is the putatively toxic entity, and hence an appropriate surrogate for interspecies and intraspecies (interindividual) scaling for the toxicokinetic component of the uncertainty factor for a Tolerable Concentration (TC) for critical hematological effects (i.e., hemolysis), the relevance of the systemic disposition of BAA to lesions of the forestomach in mice is unknown. Therefore, values for these two effects have been developed separately here, with inclusion of compound-related adjustment factors for which data are sufficient for one (hemolysis in rats) but not the other (forestomach lesions in female mice).

3.3.3.1 Hematological effects

The studies considered most appropriate for derivation of BMCs for use in characterizing the risk of hematological effects in human health associated with exposure to 2-butoxyethanol in the environment are those conducted by the NTP (1998), in which rats and mice were exposed to the substance for up to 2 years. In addition, the lowest effect levels for these endpoints were derived from these studies. In these investigations, groups of up to 50 male or female F344/N rats were exposed to concentrations of 0, 31.2, 62.5 or 125 ppm (0, 151, 302 or 604 mg/m^3) for 6 hours per day, while similar groups of B6C3F$_1$ mice were exposed to concentrations of 0, 62.5, 125 or 250 ppm (0, 302, 604 or 1208 mg/m^3). Various hematological parameters in 10 animals per exposure group were measured at several time points throughout the first 12 months of exposure. Statistically significant changes in several parameters were noted at these intervals in both species; therefore, BMC$_{05}$s were calculated for these effects, as described below. The parameters selected for exposure–response analysis were those for which there were significant changes at lowest exposure levels and for which there was some indication of a concentration-related trend. BMC$_{05}$s are presented here only for measurements made at the latest time point (i.e., 12 months), although for those parameters for which there were significant changes at earlier time points, BMC$_{05}$s were also calculated, for examination of the influence of duration on the estimates of potency.

For these hematological parameters (i.e., continuous endpoints), the BMC$_{05}$ is defined as the concentration associated with a 5% increase in the absolute risk of seeing an "adverse" response. This method utilizes the "hybrid" method of Crump (1995) to define an adverse response as the response at which 5% of the control group would be abnormal. The probability of an adverse response is then modelled, as opposed to modelling the mean response. The advantage to this method is that the BMC$_{05}$ may be calculated using the same formula as that used for discrete data.

The Weibull model was fit to each of the endpoints using BENCH_C (Crump and Van Landingham, 1996):

$$P(d) = p_0 + (1 - p_0)\left[1 - e^{-(\beta d)^k}\right]$$

where d is dose, $P(d)$ is the probability of an adverse response at dose d, and k, β and p_0 are parameters to be estimated. The BMC_{05} was then calculated as the concentration C such that

$$P(C) - P(0) = 0.05$$

Plots of the data and fitted curves are in Figure 1. Lack of fit of the model was assessed by an F-test. A p-value less than 0.05 indicates lack of fit. BMC_{05}s and the results of model fitting are displayed in Tables 6 (mice) and 7 (rats). Although the BMC_{05}s were derived on the basis of studies in which animals were exposed for a duration of less than lifetime, it was not considered appropriate to amortize exposure over a 2-year period (as is done for many chronic effects), in view of the shorter time course for formation, aging and elimination of blood cells. Values were adjusted, however, to account for non-continuous exposure of only 6 hours per day and 5 days per week by multiplying by 6/24 × 5/7 (adjusted values presented in tables).

For female mice, the model showed lack of fit for manual and automatic hematocrit and for erythrocytes. Including a threshold did not improve the model fit, so the top exposure group was eliminated. This doubled the estimated BMC_{05} for each endpoint but reduced to zero the degrees of freedom for assessing lack of fit. The model passes exactly through each of the data points, so even though a lack of fit test cannot be performed, the fit is "perfect." For rats, data for only three exposure groups were available, so the model passed directly through the data points, resulting in an F-statistic of zero and a p-value of 1.

As presented in Tables 6 and 7, the BMC_{05}s for hematological effects range from 1.1 to 12.6 ppm (5.3 to 61 mg/m^3) in rats and from 2.1 to 23.7 ppm (10 to 115 mg/m^3) in mice. In rats, the most sensitive endpoint, based solely on these estimates of potency, is the increase in mean cell hemoglobin, while in mice, the lowest BMC_{05} was that derived for increased platelets. In general, the BMC_{05}s for each parameter are lower for rats than they are for mice (although there are some exceptions in females), consistent with the observation that statistically significant changes were observed at lower concentrations in rats than in mice. Similarly, BMC_{05}s were generally lower in female rats than in male rats, which correlates with observed differences in clearance of the putatively active metabolite, BAA, in females, along with the fact that significant changes appeared earlier in females. In addition, although not presented here, BMC_{05}s determined based on measurements made at 3 and 6 months of exposure are lower in female rats than in male rats.

A TC was developed on the basis of the BMC_{05}s for hematological effects in rats, quantitatively taking into account interspecies variations in kinetics and dynamics.

PBPK models have been developed for the uptake and metabolism of 2-butoxyethanol and the circulating concentrations and renal excretion of its acetic acid metabolite, BAA (Corley *et al*., 1994; Lee *et al*., 1998), as described above in Section 2.4.3.11. Scaling of the models to humans is largely based on adjustment by (body weight)$^{0.7}$ of metabolic parameters plus appropriate physiologically based differences in organ weights and organ blood flow. These scaled parameter estimates, and the model for humans, have been validated by comparison with the limited published data on the concentrations of 2-butoxyethanol in blood and excretion of BAA in humans, for which the model was reported to provide reasonable fits.

However, a number of untested assumptions limit the utility of the model in interspecies scaling and high to low dose extrapolation. Renal elimination of BAA is assumed to be by saturable renal tubular secretion and limited by plasma protein binding. The models do not appear to allow for simple glomerular filtration of non-protein bound BAA and, more importantly, do not include any consideration of the potential for pH-dependent reabsorption from the renal tubule. The latter may well explain the apparent dose dependency in the elimination of BAA, if accumulation of this metabolite were to lead to a metabolic acidosis, which would then reduce its renal elimination.

Use of output of the models as an appropriate basis for interspecies scaling of the toxicokinetic component of adjustment factors for development of the TC can only be justified, therefore, on the basis of their mathematical validation. In fact, due to the non-validated biological assumptions inherent in the models, particularly in relation to the renal handling of the key metabolite, BAA, they add little additional value to scaling of basic kinetic parameters, such as area under the curve (AUC) or clearance, by (body weight)$^{0.7}$. Hence, a simple comparison of the AUCs for humans and experimental animals for the active metabolite is as informative for interspecies scaling.

The relevant surrogate for hematological effects is considered to be the AUC of the concentration–time relationship for the putatively toxic metabolite, BAA, since there is some evidence that duration of exposure is important and since this approach is more conservative in this case. Interspecies scaling is based, in part, on relevant data from the study in human volunteers of Johanson and Johnsson (1991). In this investigation, concentrations of BAA in blood of five healthy male human volunteers (ages not specified) were determined at 0, 2, 4 and 6 hours before and following a 2-hour exposure to 2-butoxyethanol by inhalation. Data reported in this investigation that are relevant to determination of the AUC were that the BAA level peaked after 2–4 hours and that peak concentrations were 36–46 µM (average 41) in three subjects after 2 hours and 52–60 µM (average 56) in two subjects after 4 hours; the average half-time in blood was 4.3 hours. The tabulated mean data were analyzed using a non-compartmental model and a standard kinetic program (WinNonLin) which gave an AUC of 230 µM·hour to 7.1 hours, a terminal half-life of 4.5 hours and an AUC extrapolated to infinity of 414 µM·hour. Since these relate to a 2-hour exposure to 20 ppm (97 mg/m^3), the AUC is 414/(2 x 20) = 10.4 µM·hour/ppm·hour. The PBPK model derived value for humans was not utilized since fit to the experimental data was poor.

The most appropriate study on which to base the comparative measure of the surrogate for scaling of that portion of the adjustment factor that addresses interspecies toxicokinetic variation is the investigation of Dill *et al.* (1998), in which groups of 16 male and female F344 rats (the same strain as that in the critical investigation on which the BMCs are based) were exposed to 31.2, 62.5 or 125 ppm (151, 302 or 604 mg/m^3) and 62.5, 125 or 250 ppm (302, 604 or 1208 mg/m^3), 6 hours per day, 5 days per week, respectively, for up to 18 months. Post-exposure blood samples were collected at 1 day, 2 weeks and 3, 6, 12 and 18 months; post-exposure 16-hour urine samples were collected at 2 weeks and 3, 6, 12 and 18 months of exposure. AUCs in this study were reported for the post-exposure period, only. Hence, the AUC in animals was modelled on the basis of the PBK model of Lee *et al.* (1998) by integrating the concentration of BAA in venous blood at 62.5 ppm for an inhalation time of 6 hours with a stop time of 24 hours. The resulting value was 2077.5 μM·h/(62.5*6hr) = 5.54 μM·hour/ppm·h. This result is consistent with the AUC in the post exposure period reported by the authors, being approximately twice the reported latter value.

The resulting ratio between the AUC for humans to that for rats is 10.4/5.54 or 1.9, which is approximately half of the default value for this component of 4. However, although the data on toxicokinetics in humans (restricted to five male volunteers) are sufficient as a basis for determination of a measure of central tendency for interspecies comparison, they are inadequate to inform the intraspecies (interindividual) toxicokinetic component of the uncertainty factor, which reverts to default.[6]

Information relevant to consideration of both the interspecies and intraspecies (interindividual) dynamic components of uncertainty/adjustment factors is available from several studies in which the direct effects of BAA on several measures of hemolysis in rat and human erythrocytes have been examined *in vitro* (i.e., Bartnik *et al.*, 1987; Ghanayem, 1989; Udden, 1994; Udden and Patton, 1994), as discussed above in Section 2.4.3.10. Based on these investigations, there is consistent evidence that human erythrocytes are at least 10-fold less sensitive than rat erythrocytes; therefore, the default factor for the interspecies component for dynamics (2.5) can be replaced with a value of 0.1 (and this would still be conservative). It is noteworthy that the endpoints in these studies on which this adjustment is based (haematocrit and haemoglobin concentration) are consistent with some of the endpoints in *in vivo* studies for which TCs were lowest. However, available data on intraspecies (interindividual) variation in dynamics are limited primarily to one study *in vitro* in blood from various potentially sensitive subgroups of the population in which no response was observed at the administered concentration (n = 9, 9, 7 and 3) (Udden, 1994). In several other studies, hemolysis was examined in generally pooled blood samples from unspecified or very small numbers of individuals (n = 3) as a basis solely for estimation of the central tendency for interspecies comparison (Bartnik *et al.*, 1987; Ghanayem, 1989; Udden and Patton, 1994). These data are inadequate to meaningfully quantitatively inform the replacement of default with a data-derived adjustment factor; hence, the default value of 3.2 is maintained.

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[6] For example, there is a well-recognized genetic polymorphism for alcohol dehydrogenases (the group of enzymes responsible for the first step in the metabolism of 2-butoxyethanol, i.e., oxidation to 2-butoxyaldehyde); however, while this is relevant to replacement of default for interindividual variation, the proportion of the population affected is sufficiently small (i.e., 5%) that it would not meaningfully impact on the measure of central tendency.

The total compound specific adjustment/uncertainty factor is, therefore, 1.9 (interspecies, toxicokinetic) × 0.1 (interspecies, toxicodynamic) × 3.2 (intraspecies, interindividual toxicokinetics) × 3.2 (intraspecies, interindividual toxicodynamics) = 1.9.

Based on the above considerations regarding relative sensitivity to 2-butoxyethanol-induced hematotoxicity, the TC has been derived as follows:

$$\mathrm{TC} = \frac{5.3\ \mathrm{mg/m^3}}{1.9}$$

$$\cong 2.8\ \mathrm{mg/m^3}$$

where:

- 5.3 mg/m^3 is the lower end of the range of BMCs for hematological effects in the long-term study in rats (NTP, 1998), and
- 1.9 is the compound-specific uncertainty/adjustment factor described above.

The TC for hematological effects derived based on data from investigations in experimental animals is similar to the concentration at which slight alterations in blood parameters were observed in workers (i.e., 2.2 mg/m^3), although there was no correlation with levels of butoxyacetic acid in the urine, and information on exposure was limited (Haufroid *et al*., 1997). However, in the shorter-term clinical study with internal controls (i.e., pre- and post-exposure samples), there were no effects other than irritancy at levels up to 942 mg/m^3 (Carpenter *et al*., 1956).

3.3.3.2 Other (non-hematological) effects

BMC$_{05}$s were derived for other non-cancer effects, including Kupffer cell pigmentation of the liver (although considered secondary to hemolysis), as well as ulcer and hyperplasia of the forestomach (all severities combined), based on the observations in rats and mice exposed to 2-butoxyethanol for up to 2 years (NTP, 1998). For such discrete endpoints, the BMC$_{05}$ is defined as the concentration of the substance associated with a 5% increase in incidence over background response rate. It is calculated by first fitting the following model to the exposure–response data (Howe, 1995):

$$P(d) = q_0 + (1 - q_0) \cdot \left[1 - e^{-q_1 d - \ldots - q_k d^k}\right]$$

where *d* is dose, *k* is the number of dose groups in the study, *P*(*d*) is the probability of the animal developing the effect at dose d, and $q_i > 0$, $i = 0,\ldots,k$ are parameters to be estimated.

The models were fit to the incidence data using THRESH (Howe, 1995), and the BMC_{05}s were calculated as the concentration C that satisfies

$$\frac{P(C) - P(0)}{1 - P(0)} = 0.05$$

A chi-square lack of fit test was performed for each of the model fits. The degrees of freedom for this test are equal to k minus the number of q_i's whose estimates are non-zero. A p-value less than 0.05 indicates a significant lack of fit. Resulting BMC_{05}s were adjusted for the non-constant exposure pattern by multiplying by 6/24 × 5/7.

Results from the model fitting, along with the raw BMC_{05}s and their 95% lower confidence limits (LCLs), are displayed in Table 8. Plots are shown in Figure 2. The highest dose group was dropped for forestomach ulcers in male mice because it exhibited downturn. None of the fitted models showed a significant lack of fit.

BMC_{05}s for these non-cancer endpoints range from 0.89 ppm (4.3 mg/m^3) (95% LCL = 0.73 ppm [3.5 mg/m^3]) for hyperplasia of the forestomach epithelium in female mice to 16.5 ppm (80 mg/m^3) (95% LCL = 10.9 ppm [53 mg/m^3]) for Kupffer cell pigmentation in male mice. In concordance with the greater sensitivity of rats than mice to 2-butoxyethanol-induced hemolysis, lower BMC_{05} values were determined for Kupffer cell pigmentation in rats.

A TC was developed on the basis of the lower end of the range of the BMC_{05}s for these effects (i.e., that for hyperplasia of the forestomach epithelium in female mice), although the range of these values is relatively small. In addition, hemosiderin pigmentation is considered to be secondary to hemolysis, rather than an adverse effect directly associated with exposure to 2-butoxyethanol. The TC was developed as follows:

$$\text{TC} = \frac{4.3\ \text{mg/m}^3}{100}$$

$$\cong 0.04\ \text{mg/m}^3$$

where:

- 4.3 mg/m^3 is the BMC associated with a 5% increase in the incidence of hyperplasia of the forestomach epithelium in female $B6C3F_1$ mice exposed to 2-butoxyethanol for 2 years (NTP, 1998), and

- 100 is the uncertainty factor (×10 for intraspecies variation and ×10 for interspecies variation). Available data are considered insufficient to allow default values for intra- and interspecies variations in toxicokinetics and toxicodynamics to be replaced by data-derived values — i.e., the potential role of the putatively toxic metabolite in the induction of local irritant effects is unknown, and relative sensitivity has not been investigated.

This TC for forestomach lesions is considered to be protective for squamous cell papillomas or carcinomas of the forestomach in mice for which tumorigenic potencies have been estimated using multistage modelling (Global82; Howe and Crump, 1982). TCs derived on the basis of the incidence of tumours at other sites, although the weight of evidence for an association with 2-butoxyethanol is considered quite limited, are greater than those for tumours of the forestomach.

It is noteworthy that the TC based on forestomach lesions is 70-fold lower than that derived for 2-butoxyethanol-induced hematological effects. However, it is important to keep in mind that the BMC_{05}s for non-neoplastic lesions in the forestomach were derived on the basis of the incidences of lesions of all severities (combined), including those considered to be minimal. In addition, the association between exposure to 2-butoxyethanol and hemolysis has been much more thoroughly investigated than the association with effects on the forestomach, with some evidence (albeit quite weak) of hematological effects in humans.

3.3.4 Risk characterization

As discussed above, based on the limited data available on levels of 2-butoxyethanol in environmental media, inhalation in air appears to be a principal route of exposure to 2-butoxyethanol for the general population in Canada. The mean concentration of 2-butoxyethanol in outdoor air reported in the multimedia exposure study was 8.4 $\mu g/m^3$, with a maximum of 243 $\mu g/m^3$. However, as discussed below, the confidence in these values is low, due to the analytical methodology employed, although they are considered conservative. Indeed, in the only other Canadian study identified (in which the confidence is greater), the maximum outdoor air concentration reported near a likely source (an automotive plant) was lower (i.e., 7.3 $\mu g/m^3$). Exposure in indoor air is generally greater than that in outdoor air. In the multimedia exposure study, the mean concentration of 2-butoxyethanol in 50 samples from Canadian residences was 27.5 $\mu g/m^3$, with a maximum measured concentration of 438 $\mu g/m^3$. However, exposure to 2-butoxyethanol through use of some consumer products could be much higher. For example, conservative estimates of indoor air concentrations resulting from emissions of some products recently investigated in Canada range up to 446 mg/m^3, while upper-bounding estimates of indoor air concentrations that could result from use of paints or paint thinners containing 2-butoxyethanol range up to 18 390 mg/m^3.

Based on evaluation of available data (principally toxicological investigations in experimental animals), hematotoxicity is considered the principal effect for characterization of potential risk to humans associated with exposure to 2-butoxyethanol. As described above, a TC of 2.8 mg/m^3 (2800 $\mu g/m^3$)

was derived for 2-butoxyethanol on the basis of BMCs determined for alterations in hematological parameters based on the observations in rats and mice following long-term exposure, taking into consideration interspecies differences in toxicokinetics and toxicodynamics. A more conservative TC of 0.04 mg/m^3 (40 µg/m^3) was also derived for co-critical forestomach lesions reported in chronically exposed mice, although confidence in this latter value is less, for the reasons outlined in Section 3.3.5.

Comparison of measured exposure levels in outdoor air with the TCs indicates that average exposure in the ambient environment does not exceed either the TC for hematological effects (in which there is greater confidence) or the more conservative TC for lesions of the forestomach. However, the maximum concentration reported in outdoor air in the multimedia exposure study exceeds the lesser of these TCs (i.e., for forestomach lesions), although confidence in both these values is lower. Likewise, mean concentrations in indoor air reported in the multimedia exposure study are less than the TCs, while the maximum level reported again exceeds the more conservative TC.

The elevated exposure in indoor air is likely due to use of consumer products containing 2-butoxyethanol. Indeed, crude estimates of exposure through direct use of such products, although based on limited data, greatly exceed the TCs for adverse health effects. The maximum estimated indoor air concentration of 2-butoxyethanol based on monitored emissions from products is about four orders of magnitude greater than the more conservative TC for forestomach lesions; the margin between this predicted indoor air concentration resulting from emissions from consumer products and the TC in which confidence is greater (i.e., hematological effects) is approximately 160. However, estimated indoor concentrations from use of paints or paint thinner containing 2-butoxyethanol, although based on very limited data and several conservative assumptions, exceed even the less conservative TC, in which confidence is higher, by up to four orders of magnitude.

Acquisition of additional data on the content of 2-butoxyethanol in consumer products currently available in Canada and emissions from these products is considered to be a high priority.

3.3.5 Uncertainties and degree of confidence in the human health risk characterization

There is a high degree of uncertainty in the estimates of population exposure that have been developed for this assessment, due to the paucity of data on levels of 2-butoxyethanol in environmental media. Although estimates of average and worst-case exposures were based on data reported in the multimedia exposure study conducted in Canada, the methodology employed in this study is considered experimental, and confidence in the results is considered to be low. For example, recovery was relatively low (i.e., 52% in air), and concentrations in "blanks" were high; moreover, non-standard desorbing solvents were used to extract 2-butoxyethanol from environmental samples. However, the concentrations reported can be considered to be conservative, based on comparison with the lower concentrations reported in outdoor air near a potential point source in Windsor, Ontario. In addition, there is a moderate degree of uncertainty concerning the relative contribution of food to total intake of

2-butoxyethanol, as no relevant monitoring data were identified, and this might be an appropriate area of additional investigation.

For those products where monitoring of emissions was conducted, confidence in estimated exposures is low to moderate. Confidence in the estimated exposures from consumer products for which monitoring data on emissions were not available is considered to be very low, based on the paucity of data on concentrations of 2-butoxyethanol in products currently used in Canada. However, based on the few products recently investigated at Health Canada, indoor air concentrations of 2-butoxyethanol predicted from measured emissions are similar to levels estimated on the basis of product use scenarios, limited information on product composition and the conservative assumption of complete transfer from the product to air. Acquisition of additional data on the content of 2-butoxyethanol in consumer products currently available in Canada and its emissions from these products is considered to be a high priority.

There is a moderate degree of certainty that hematotoxicity is the principal critical endpoint for 2-butoxyethanol, based on the observations in short- and long-term studies in multiple species of experimental animals. However, there is only limited evidence that 2-butoxyethanol induces hematological effects in humans; in fact, available data from *in vitro* investigations suggest that humans may be less sensitive than rats, which appear to be the most sensitive laboratory species identified to date. This lesser sensitivity of humans compared with rats with respect to hematological effects is accounted for in the small uncertainty factor applied to the BMC_{05} in the derivation of the TC, and limited available data from studies in humans indicated that the TC is protective. Although the component for interspecies toxicokinetics of the total compound specific adjustment/uncertainty factor was based on data for a limited number of time points, this value is approximately only 2-fold less than the default for this component. However, the database for the component that considerably impacts on deviation from default for the uncertainty factor (i.e., that of interspecies variations in dynamics) is much more extensive.

However, it should be noted that no data were available on the effects of 2-butoxyethanol on hematological parameters in rodents in the critical studies past 12 months. In addition, the sizes of the groups of animals in which blood was examined at each time point were small.

The TC was derived on the basis of point estimates for the BMCs, as opposed to the 95% LCLs; however, use of the LCLs would not change the TC substantially, since for most parameters, the LCL was less than 3-fold lower than the midpoint estimate. In addition, if the BMCs for hematological effects had been determined on the basis that 10% of the control population was considered "abnormal" (as opposed to 5% used in derivations presented), the resulting values would vary by less than 1.5-fold.

There is a moderate to high amount of uncertainty concerning the TC derived on the basis of the BMC for lesions of the forestomach in mice (although these effects were consistently observed in subchronic studies in rats and mice and in the only chronic study in mice). Although the profile of effects suggests a progression from irritation to ulceration and tumour formation, due to the lack of information on the mode of induction of these lesions, including the role of putatively toxic metabolites, their relevance to humans is unknown but cannot be precluded. If these lesions are local effects resulting from ingestion, mice are likely to be considerably more sensitive due to longer residence time in the mice forestomach (and its low acidity) compared to the human oesophagus. Because the animals were exposed to 2-butoxyethanol via inhalation, preening may have contributed to exposure at the target site. If ingestion via preening or mucociliary clearance were significant, then the TC based on BMCs derived on the basis of the airborne exposure concentrations would likely overestimate the risk to humans (i.e., there would not be the additional exposure via ingestion). On the other hand, dermal absorption of airborne 2-butoxyethanol by humans (which could be significant) has also not been considered in the determination of the TC.

3.4 Proposed conclusions

CEPA 1999 64(a): Based on conservative estimates of exposure and effects in Canada, risk quotients for terrestrial wildlife, soil organisms and aquatic organisms are less than one. The environmental risks associated with estimated concentrations of 2-butoxyethanol likely to be found in Canada therefore appear to be low. Therefore, available data indicate that it is unlikely that 2-butoxyethanol is entering the environment in a quantity or concentration or under conditions that have or may have an immediate or long-term harmful effect on the environment or its biological diversity, and it is proposed that it should not be considered "toxic" as defined in CEPA 1999 Paragraph 64(a).

CEPA 1999 64(b): 2-Butoxyethanol is not involved in the depletion of stratospheric ozone and likely does not contribute significantly to climate change. Because of its very low estimated concentration in air in Canada, it is unlikely to play a significant role in tropospheric ozone production. Therefore, based on available data, it has been concluded that 2-butoxyethanol is not entering the environment in a quantity or concentration or under conditions that constitute or may constitute a danger to the environment on which life depends, and it is proposed that it should not be considered "toxic" as defined in CEPA 1999 Paragraph 64(b).

CEPA 1999 64(c): Based on available data, 2-butoxyethanol is considered to be entering the environment in a quantity or concentration or under conditions that constitute or may constitute a danger in Canada to human life or health. Therefore, it is proposed that 2-butoxyethanol be considered "toxic" as defined in CEPA 1999 Paragraph 64(c).

Proposed overall conclusion: Based on critical assessment of relevant information, it is proposed that 2-butoxyethanol be considered "toxic" as defined in Section 64 of CEPA 1999.

3.5 Considerations for follow-up (further action)

Additional characterization of the ranges and distributions of concentrations of 2-butoxyethanol in consumer products currently available in Canada and their emissions is considered a clear priority as a basis for risk management.

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Table 1: Effects of concentration and time on hematocrit and the concentration of free plasma hemoglobin in rat blood incubated with butoxyacetic acid (BAA) *in vitro* (data from Ghanayem, 1989)

	Time since exposure (hours)				
	0.25	0.5	1.0	2.0	4.0
Hematocrit (% control)					
0.5 mM BAA		104	108	110	121
1.0 mM BAA		111	117	124	144
2.0 mM BAA	111	118	133	169	<10
Plasma hemoglobin (g/dL)					
0.5 mM BAA		0.2	0.2	0.2	0.5
1.0 mM BAA		0.4	0.8	1.0	2.0
2.0 mM BAA		0.6	1.0	2.2	7.0

Table 2: Effects of concentration, time and sex on hematocrit and the concentration of free plasma hemoglobin in human blood incubated with butoxyacetic acid (BAA) *in vitro* (data from Ghanayam, 1989)

	Time since exposure (hours)					
	Males			Females		
	1.0	2.0	4.0	1.0	2.0	4.0
Hematocrit (% control)						
2.0 mM BAA	100.8	102.5	103.2	98.6	100.0	100.2
4.0 mM BAA	102.0	103.0	104.8	100.2	100.8	103.0
8.0 mM BAA	104.0	105.1	108.2	103.6	104.0	106.4
Plasma hemoglobin (g/dL)						
2.0 mM BAA	0.12	0.13	0.20	0.14	0.15	0.17
4.0 mM BAA	0.17	0.22	0.30	0.20	0.25	0.25
8.0 mM BAA	0.40	0.42	0.53	0.35	0.39	0.44

Table 3: Estimated average intake of 2-butoxyethanol by six age groups in the general population

Route of exposure	Estimated average intake of 2-butoxyethanol by various age groups in the general population (µg/kg-bw per day)					
	0–6 months[1]	7 months–4 years[2]	5–11 years[3]	12–19 years[4]	20–59 years[5]	60+ years[6]
Ambient air[7]	0.3	0.6	0.5	0.3	0.2	0.2
Indoor air[8] (inhalation)	6.7	14	11	6.4	5.5	4.8
Indoor air[8] (dermal)	0.9	0.7	0.5	0.5	0.4	0.4
Drinking water[9]	0.2[10]	0.01	0.01	<0.01	<0.01	<0.01
Subtotal	**8.1**	**15**	**12**	**7.2**	**6.1**	**5.4**

[1] Assumed to weigh 7.5 kg, to drink 0.8 L of water per day, to breathe 2.1 m^3 of air per day (EHD, 1998) and to have a skin surface area of 3680 cm^2 (Health Canada, 1995).

[2] Assumed to weigh 15.5 kg, to drink 0.70 L of water per day, to breathe 9.3 m^3 of air per day (EHD, 1998) and to have a skin surface area of 5780 cm^2 (Health Canada, 1995).

[3] Assumed to weigh 31.0 kg, to drink 1.1 L of water per day, to breathe 14.5 m^3 of air per day (EHD, 1998) and to have a skin surface area of 9660 cm^2 (Health Canada, 1995).

[4] Assumed to weigh 59.4 kg, to drink 1.2 L of water per day, to breathe 15.8 m^3 of air per day (EHD, 1998) and to have a skin surface area of 16 200 cm^2 (Health Canada, 1995).

[5] Assumed to weigh 70.9 kg, to drink 1.5 L of water per day, to breathe 16.2 m^3 of air per day (EHD, 1998) and to have a skin surface area of 18 200 cm^2 (Health Canada, 1995).

[6] Assumed to weigh 72.0 kg, to drink 1.6 L of water per day, to breathe 14.3 m^3 of air per day (EHD, 1998) and to have a skin surface area of 18 200 cm^2 (Health Canada, 1995).

[7] Based on the mean concentration of 2-butoxyethanol in samples of ambient air collected outside of 50 Canadian residences, 8.4 $\mu g/m^3$ (Conor Pacific Environmental Technologies Inc., 1998). 2-Butoxyethanol was not detected in 68% of these ambient air samples. A concentration of 0.42 $\mu g/m^3$ (one-half the detection limit of 0.84 $\mu g/m^3$) was assumed for the samples in which 2-butoxyethanol was not detected. Each age group is assumed to spend an average of 3 hours per day outdoors.

[8] Based on the mean concentration of 2-butoxyethanol in 50 indoor air samples collected in Canadian residences, 27.5 $\mu g/m^3$ (Conor Pacific Environmental Technologies Inc., 1998). 2-Butoxyethanol was not detected in 34% of these indoor air samples. A concentration of 0.42 $\mu g/m^3$ (one-half the detection limit of 0.84 $\mu g/m^3$) was assumed for the samples in which 2-butoxyethanol was not detected. The average daily intake of 2-butoxyethanol from indoor air via dermal uptake was calculated by combining the mean indoor air concentration of 27.5 $\mu g/m^3$ from the Canadian multimedia study, air intake rates and body weight data from EHD (1998), surface area estimates from Health Canada (1995), and a mean permeability coefficient of 3 cm/hour taken from Corley*et al.* (1997). Each age group is assumed to spend an average of 21 hours per day indoors.

[9] Based on the mean concentration of 2-butoxyethanol in drinking water in 50 drinking water samples collected at Canadian residences, 0.18 µg/L (detection limit 0.02 µg/L; frequency of detection 0.68). A concentration of 0.01 µg/L (one-half the detection limit of 0.02 µg/L) was assumed for the samples in which 2-butoxyethanol was not detected.

[10] Based on the assumption that infants were exclusively formula fed and consumed 800 ml of formula that was prepared with tap water (EHD, 1998).

Note: Insufficient data were available to estimate intake from soil or food.

Table 4: Reasonable worst-case intake of 2-butoxyethanol by six age groups in the general population

Route of exposure	Reasonable worst-case intake of 2-butoxyethanol by various age groups in the general population (μg/kg-bw per day)					
	0–6 months[1]	7 months–4 years[2]	5–11 years[3]	12–19 years[4]	20–59 years[5]	60+ years[6]
Ambient air[7]	8.5	18	14	8.1	6.9	6.0
Indoor air[8] (inhalation)	107	230	179	102	88	76
Indoor air[8] (dermal)	18	14	12	10	9.5	9.3
Drinking water[9]	0.5[10]	0.2	0.2	0.1	0.1	0.1
Subtotal	**134**	**262**	**205**	**120**	**105**	**91**

[1] Assumed to weigh 7.5 kg, to drink 0.8 L of water per day, to breathe 2.1 m^3 of air per day (EHD, 1998) and to have a skin surface area of 3680 cm^2 (Health Canada, 1995).

[2] Assumed to weigh 15.5 kg, to drink 0.70 L of water per day, to breathe 9.3 m^3 of air per day (EHD, 1998) and to have a skin surface area of 5780 cm^2 (Health Canada, 1995).

[3] Assumed to weigh 31.0 kg, to drink 1.1 L of water per day, to breathe 14.5 m^3 of air per day (EHD, 1998) and to have a skin surface area of 9660 cm^2 (Health Canada, 1995).

[4] Assumed to weigh 59.4 kg, to drink 1.2 L of water per day, to breathe 15.8 m^3 of air per day (EHD, 1998) and to have a skin surface area of 16 200 cm^2 (Health Canada, 1995).

[5] Assumed to weigh 70.9 kg, to drink 1.5 L of water per day, to breathe 16.2 m^3 of air per day (EHD, 1998) and to have a skin surface area of 18 200 cm^2 (Health Canada, 1995).

[6] Assumed to weigh 72.0 kg, to drink 1.6 L of water per day, to breathe 14.3 m^3 of air per day (EHD, 1998) and to have a skin surface area of 18 200 cm^2 (Health Canada, 1995).

[7] Based on the maximum concentration of 2-butoxyethanol in 50 ambient air samples collected outside of Canadian residences, 243 $\mu g/m^3$ (Conor Pacific Environmental Technologies Inc., 1998).

[8] Based on the maximum concentration of 2-butoxyethanol in 50 indoor air samples collected in Canadian residences, 438 $\mu g/m^3$ (Conor Pacific Environmental Technologies Inc., 1998). The average daily intake of 2-butoxyethanol from indoor air via dermal uptake was calculated by combining the maximum indoor air concentration of 438 $\mu g/m^3$ from the Canadian multimedia study, air intake rates and body weight data from EHD (1998), surface area estimates from Health Canada (1995), and a maximum permeability coefficient of 4 cm/hour taken from Corley *et al.* (1997).

[9] Based on the maximum concentration of 2-butoxyethanol in 29 drinking water samples collected in Ontario, 5.0 μg/L (OMEE, 1996).

[10] Based on the assumption that infants were exclusively formula fed and consumed 800 ml of formula that was prepared with tap water (EHD, 1998).

Note: Insufficient data were available to estimate intake from soil or food.

Table 5: Upper-bounding estimates of daily intake of 2-butoxyethanol from consumer products

Exposure medium	Assumptions	Estimated intake per event (mg/kg-bw per event)	Estimated average daily intake (mg/kg-bw per day)
EXPOSURE BASED ON DATA ON EMISSIONS FROM PRODUCTS			
All-purpose liquid cleaner	**Inhalation** - the range of concentrations in a standard room was calculated to be 134–446 mg/m ^{3} based on a measured average emission rate (Cao, 1999), an emitting surface area of 1 m ^{2}, a room volume of 17.4 m^3 and an air exchange rate of 0.18 per hour - assuming a 0.47-hour duration of exposure, a breathing rate of 1.3 m^3/hour for an average adult during light-level activity and a frequency of use of 360 days per year (Versar Inc., 1986) - a body weight of 70.9 kg is assumed for an average Canadian adult (EHD, 1998) $\frac{(446\ \text{mg/m}^3)\ (0.47\ \text{hour})\ (360/365\ \text{days})\ (1.3\ \text{m}^3\text{/hour})}{(70.9\ \text{kg})}$	3.8 [estimated maximum indoor air concentration of 446 mg/m ^{3}]	3.8
Glass cleaner	**Inhalation** - the range of concentrations in a standard room was calculated to be 45–128 mg/m ^{3} based on a measured average emission rate (Cao, 1999), an emitting surface area of 1 m ^{2}, a room volume of 17.4 m^3 and an air exchange rate of 0.18 per hour - assuming a 0.47-hour duration of exposure, a breathing rate of 1.3 m^3/hour for an average adult during light-level activity and a frequency of use of 360 days per year (Versar Inc., 1986) - a body weight of 70.9 kg is assumed for an average Canadian adult (EHD, 1998) $\frac{(128\ \text{mg/m}^3)\ (0.47\ \text{hour})\ (360/365\ \text{days})\ (1.3\ \text{m}^3\text{/hour})}{(70.9\ \text{kg})}$	1.1 [estimated maximum indoor air concentration of 128 mg/m ^{3}]	1.1

Exposure medium	Assumptions	Estimated intake per event (mg/kg-bw per event)	Estimated average daily intake (mg/kg-bw per day)
Nail polish remover	**Inhalation** - the concentration in a standard room was calculated to be 19 mg/m ^{3} based on a measured average emission rate (Cao, 1999), an emitting surface area of 0.09 m ^{2}, a room volume of 17.4 m ^{3} and an air exchange rate of 0.18 per hour - assuming a 0.25-hour duration of exposure, a frequency of use of 0.29/day (ECETOC, 1990) and a breathing rate of 1.3 m ^{3}/hour for an average adult during light-level activity (Versar Inc., 1986) - a body weight of 70.9 kg is assumed for an average Canadian adult (EHD, 1998) $\frac{(19\ \mathrm{mg/m^3})\ (0.25\ \mathrm{hour})\ (0.29/\mathrm{day})\ (1.3\ \mathrm{m^3/hour})}{(70.9\ \mathrm{kg})}$	0.087 [estimated indoor air concentration of 19 mg/m ^{3}]	0.025
Permanent hair colorant	**Inhalation** - the concentration in a standard room was calculated to be 25 mg/m ^{3} based on a measured average emission rate (Cao, 1999), an emitting surface area of 0.13 m ^{2}, a room volume of 17.4 m ^{3} and an air exchange rate of 0.18 per hour - assuming a 0.5-hour duration of exposure, a frequency of use of 0.033/day (ECETOC, 1990) and a breathing rate of 1.3 m ^{3}/hour for an average adult during light-level activity (Versar Inc., 1986) - a body weight of 70.9 kg is assumed for an average Canadian adult (EHD, 1998) $\frac{(25\ \mathrm{mg/m^3})\ (0.5\ \mathrm{hour})\ (0.033/\mathrm{day})\ (1.3\ \mathrm{m^3/hour})}{(70.9\ \mathrm{kg})}$	0.23 [estimated indoor air concentration of 25 mg/m ^{3}]	0.008
EXPOSURE BASED ON PRODUCT COMPOSITION			

Exposure medium	Assumptions	Estimated intake per event (mg/kg-bw per event)	Estimated average daily intake (mg/kg-bw per day)
Nail polish	**Dermal**[1] - based on the upper bound of the concentration range of >3–10% of 2-butoxyethanol in nail polish - assumed a typical quantity of product used per event for "nail polish & enamel" of 0.28 g and a maximum event frequency of 0.71 times per day for users only (U.S. EPA, 1997) - a body weight of 70.9 kg is assumed for an average Canadian adult (EHD, 1998) $\frac{(0.10)\,(0.28\text{ g})\,(0.71/\text{day})\,(1000\text{ mg/g})}{(70.9\text{ kg})}$	0.4	0.3
Nail polish remover	**Dermal**[1] - based on the upper bound of the concentration range of >3–10% of 2-butoxyethanol in nail polish remover - assumed a typical quantity of product used per event for "nail polish & enamel remover" of 3.06 g and a maximum event frequency of 0.29 times per day for users only (U.S. EPA, 1997) - a body weight of 70.9 kg is assumed for an average Canadian adult (EHD, 1998) $\frac{(0.10)\,(3.06\text{ g})\,(0.29/\text{day})\,(1000\text{ mg/g})}{(70.9\text{ kg})}$	4.3	1.3

Exposure medium	Assumptions	Estimated intake per event (mg/kg-bw per event)	Estimated average daily intake (mg/kg-bw per day)
Hair dye	**Dermal**[1] - maximal time-dependent estimate based on rinse-off nature of application - based on the upper bound of the concentration range of >3–10% of 2-butoxyethanol in hair dye, which is left on the head for 30 minutes and then rinsed off. The maximum frequency of events per day, for users only, is 0.033 (once per month) (ECETOC, 1990) - the estimated maximum hourly permeation rate is assumed to be within a range of 138–198 µg/cm ^{2} per hour (mean range of dermal uptake of 2-butoxyethanol from *in vivo* and *in vitro* studies by Johanson *et al* [1988] and Bartnik *et al* [1987]) - a body weight of 70.9 kg (EHD, 1998) and a surface area of the head of 1275 cm ^{2} (Health Canada, 1995) are assumed for an average Canadian adult $\frac{(0.10)\ (0.138\text{–}0.198\ \text{mg/cm}^2\ \text{per hour})\ (1275\ \text{cm}^2)\ (0.5\ \text{hour})\ (0.033/\text{day})}{(70.9\ \text{kg})}$	0.1–0.2	0.004–0.006
All-purpose liquid cleaner	**Inhalation**[2] - based on a maximum concentration of 10% 2-butoxyethanol in all-purpose liquid cleaner (Flick, 1986, 1989) - assuming a mass of 35 g is used per event, a 0.47-hour duration of exposure, a room volume of 20 m ^{3}, a breathing rate of 1.3 m ^{3}/hour for an average adult during light-level activity, and a frequency of use of 360 days per year (Versar Inc., 1986) - a body weight of 70.9 kg is assumed for an average Canadian adult (EHD, 1998) $\frac{(0.10)\ (360/365\ \text{days})\ (35\,000\ \text{mg})\ (0.47\ \text{hour})\ (1.3\ \text{m}^3/\text{hour})}{(20\ \text{m}^3)\ (70.9\ \text{kg})}$	1.5 [estimated indoor air concentration of 175 mg/m ^{3}]	1.5

Exposure medium	Assumptions	Estimated intake per event (mg/kg-bw per event)	Estimated average daily intake (mg/kg-bw per day)
	Dermal[1] - based on a maximum concentration of 10% 2-butoxyethanol in all-purpose liquid cleaner (Flick, 1986, 1989) - assuming an event frequency of 360 days per year, an exposed surface area of 400 cm ^{2} (both palms), a product density of 1.19 g/cm ^{3} and a film thickness on the hands of 2.1 × 10 $^{-3}$ cm (Versar Inc., 1986) - a body weight of 70.9 kg is assumed for an average Canadian adult (EHD, 1998) $\frac{(0.10)(360/365\text{ days})(400\text{ cm}^2)(1190\text{ mg/cm}^3)(2.1\times10^{-3}\text{ cm})}{(70.9\text{ kg})}$	1.4	1.4
All-purpose spray cleaner	**Inhalation**[2] - based on a maximum concentration of 10% 2-butoxyethanol in all-purpose spray cleaner (Flick, 1986, 1989) - assuming a mass of 76 g is used per event, a 0.47-hour duration of exposure, a room volume of 20 m ^{3}, a breathing rate of 1.3 m^3/hour for an average adult during light-level activity and a frequency of use of 360 days per year (Versar Inc., 1986) - a body weight of 70.9 kg is assumed for an average Canadian adult (EHD, 1998) $\frac{(0.10)(360/365\text{ days})(76\,000\text{ mg})(0.47\text{ hour})(1.3\text{ m}^3\text{/hour})}{(20\text{ m}^3)(70.9\text{ kg})}$	3.3 [estimated indoor air concentration of 380 mg/m ^{3}]	3.2

Exposure medium	Assumptions	Estimated intake per event (mg/kg-bw per event)	Estimated average daily intake (mg/kg-bw per day)
	Dermal[1] - based on a maximum concentration of 10% 2-butoxyethanol in all-purpose spray cleaner (Flick, 1986, 1989) - assuming an event frequency of 360 days per year, an exposed surface area of 400 cm^2 (both palms), a product density of 0.88 g/cm^3 and a film thickness on the hands of 2.1×10^{-3} cm (Versar Inc., 1986) - a body weight of 70.9 kg is assumed for an average Canadian adult (EHD, 1998) $\frac{(0.10)\ (360/365\ days)\ (400\ cm^2)\ (880\ mg/cm^3)\ (2.1 \times 10^{-3}\ cm)}{(70.9\ kg)}$	1.0	1.0
Latex or oil-based paints	**Inhalation**[2] - based on a maximum concentration of 6% 2-butoxyethanol in paint (Plehn, 1990) - assuming a mass of 6130 g is used per event, a 5.5-hour duration of exposure, a room volume of 20 m^3, a breathing rate of 1.3 m^3/hour for an average adult during light-level activity and a frequency of use of 7 days per year (Versar Inc., 1986) - a body weight of 70.9 kg is assumed for an average Canadian adult (EHD, 1998) $\frac{(0.06)\ (7/365\ days)\ (6\ 130\ 000\ mg)\ (5.5\ hour)\ (1.3\ m^3/hour)}{(20\ m^3)\ (70.9\ kg)}$	1855 [estimated indoor air concentration of 18 390 mg/m^3]	36

Exposure medium	Assumptions	Estimated intake per event (mg/kg-bw per event)	Estimated average daily intake (mg/kg-bw per day)
	Dermal[1] - based on a maximum concentration of 6% 2-butoxyethanol in paint (Plehn, 1990) - assuming an event frequency of 7 days per year, an exposed surface area of 220 cm^2 (10% of face, hands and forearms), a film thickness on the hands of 9.81×10^{-3} cm and a product density of 1240 mg/cm^3 (Versar Inc., 1986) - a body weight of 70.9 kg is assumed for an average Canadian adult (EHD, 1998) $\frac{(0.06)\ (7/365\ days)\ (220\ cm^2)\ (1240\ mg/cm^3)\ (9.81 \times 10^{-3}\ cm)}{(70.9\ kg)}$	2.3	0.04
Paint thinner	**Inhalation**[2] - based on a maximum concentration of 30% 2-butoxyethanol in paint thinner (General Paint Ltd., 1997) - assuming a mass of 5430 g is used per event, a 0.5-hour duration of exposure, a room volume of 125 m^3, a breathing rate of 1.3 m^3/hour for an average adult during light-level activity and a frequency of use of 48 days per year (Versar Inc., 1986) - a body weight of 70.9 kg is assumed for an average Canadian adult (EHD, 1998) $\frac{(0.30)\ (48/365\ days)\ (5\,430\,000\ mg)\ (0.5\ hour)\ (1.3\ m^3/hour)}{(125\ m^3)\ (70.9\ kg)}$	119 [estimated indoor air concentration of 13 032 mg/m^3]	16

Exposure medium	Assumptions	Estimated intake per event (mg/kg-bw per event)	Estimated average daily intake (mg/kg-bw per day)
	Dermal[1] - based on a maximum concentration of 30% 2-butoxyethanol in paint thinner (General Paint Ltd., 1997) - assuming an event frequency of 48 days per year, an exposed surface area of 795 cm^2 (both hands), a film thickness on the hands of 3.25×10^{-3} cm and a product density of 0.80 g/cm^3 (Versar Inc., 1986) - a body weight of 70.9 kg is assumed for an average Canadian adult (EHD, 1998) $\frac{(0.30)\ (48/365\ \text{days})\ (795\ \text{cm}^2)\ (800\ \text{mg/cm}^3)\ (3.25 \times 10^{-3}\ \text{cm})}{(70.9\ \text{kg})}$	8.7	1.2

[1] Estimates of intake by dermal absorption of 2-butoxyethanol in liquid consumer products are based on the assumptions that a portion of the skin contacts the liquid and the amount absorbed is directly proportional to the area of exposed skin. It is assumed that all of the ingredient present in the liquid is absorbed through the skin. Standard exposure scenarios for dermal absorption of ingredients of liquid consumer products (e.g., Versar Inc., 1986; U.S. EPA, 1997) often include recommended skin surface areas and surface film thickness, depending on the type of product and the manner in which it is used. For example, in Versar Inc. (1986), surface areas assumed are 400 cm^2 for both palms of adult hands for scenarios involving some liquid cleaning products and 220 cm^2 for the portion (i.e., 10%) of the skin surface area of the face, hands and forearms of an average size adult that can potentially be covered with paint splatter during application of latex paint. Experimental data for surface film thickness are often not available for some types of consumer products and are estimated by analogy with other liquid substances.

[2] Estimates of intake by inhalation are based on the assumptions that the ingredient is completely and instantaneously released from the applied product, the concentration is homogenous throughout the assumed volume, and no air exchange occurs between this volume and adjacent areas. Standard exposure scenarios for inhalation intakes of volatile ingredients of consumer products used in indoor spaces (e.g., Versar Inc., 1986; U.S. EPA, 1997) often include recommended room volumes intended to be representative of the areas within a residence where the products are typically used. For example, in Versar Inc. (1986), a room volume of 20 m^3 is assumed for tasks involving all-purpose liquid and spray cleaners and paints, whereas a larger volume of 125 m^3 is recommended for the use of lacquer thinner, since the task of cleaning up is assumed to take place in a basement area, rather than within a room in the house.

Table 6: BMC$_{05}$s and model fitting information for hematological effects in mice

	BMC$_{05}$ (ppm)	95% LCL (ppm)	F statistic	df	p-value
Male mice					
Automated hematocrit	18.6	9.1	1.13	1,35	0.30
Manual hematocrit	19.6	8.9	0.51	1,35	0.48
Hemoglobin	17.1	7.2	0.88	1,35	0.35
Erythrocytes	23.7	9.4	0.19	1,35	0.66
Platelets	2.1	1.0	1.89	1,35	0.18
Female mice					
Automated hematocrit[1]	11.6	6.1	0	0,36	1.00
Manual hematocrit[1]	10.1	5.3	0	0,36	1.00
Hemoglobin	3.4	1.6	2.54	1,36	0.12
Erythrocytes[1]	9.4	4.9	0	0,36	1.00
Mean cell volume	12.6	2.4	0.34	1,36	0.56
Platelets	8.6	1.9	1.82	1,36	0.19

[1] Highest dose group excluded to eliminate downturn from dose–response relationship.

Table 7: BMC$_{05}$s and model fitting information for hematological effects in rats

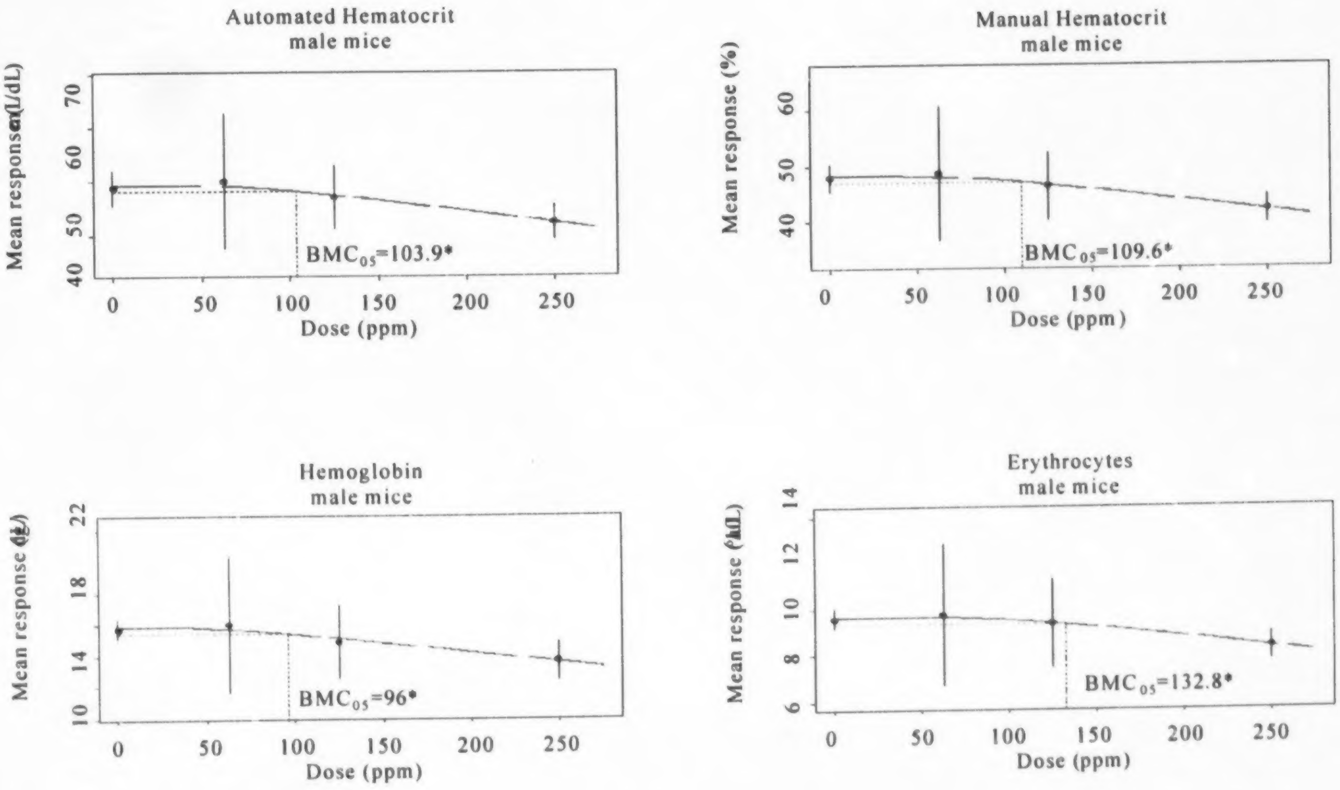
	BMC$_{05}$ (ppm)	95% LCL (ppm)	F statistic	df	p-value
Male rats					
Automated hematocrit	6.9	1.3	0	0,23	1.00
Manual hematocrit	7.3	1.1	0	0,23	1.00
Hemoglobin	8.0	3.7	0	0,23	1.00
Erythrocytes	6.6	2.8	0	0,23	1.00
Reticulocytes	12.6	2.1	0	0,23	1.00
Mean cell volume	7.1	4.6	0	0,23	1.00
Mean cell hemoglobin	6.1	1.6	0	0,23	1.00
Female rats					
Automated hematocrit	9.3	6.3	0	0,23	1.00
Manual hematocrit	12.3	12.1	0	0,23	1.00
Hemoglobin	7.9	5.0	0	0,23	1.00
Erythrocytes	3.9	2.3	0	0,23	1.00
Reticulocytes	3.0	1.1	0	0,23	1.00
Mean cell volume	1.7	0.27	0	0,23	1.00
Mean cell hemoglobin	1.1	0.23	0	0,23	1.00

Table 8: BMC_{05}s and model fitting information for other non-hematological endpoints

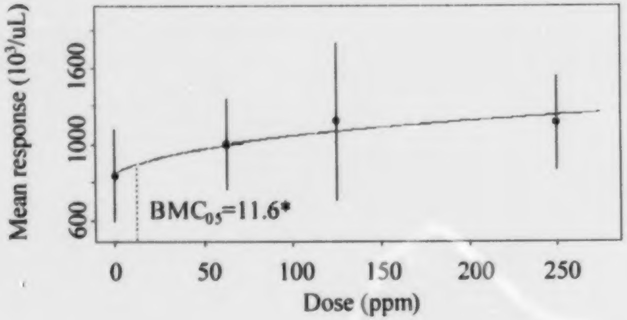
	BMC_{05} (ppm)	95% LCL (ppm)	Chi-square	df	p-value
Kupffer cell pigmentation (male rats)	1.1	0.68	0.05	1	0.82
Kupffer cell pigmentation (female rats)	2.2	0.68	1.44	1	0.23
Forestomach ulcer (male mice)[1]	12.4	5.8	0.35	1	0.55
Hyperplasia of forestomach epithelium (male mice)	3.9	3.0	0.97	2	0.61
Forestomach ulcer (female mice)	4.3	3.2	0.001	1	0.91
Hyperplasia of forestomach epithelium (female mice)	0.89	0.73	4.05	2	0.13
Kupffer cell pigmentation (male mice)	16.5	10.9	1.84	1	0.17
Kupffer cell pigmentation (female mice)	6.6	2.9	1.77	2	0.41

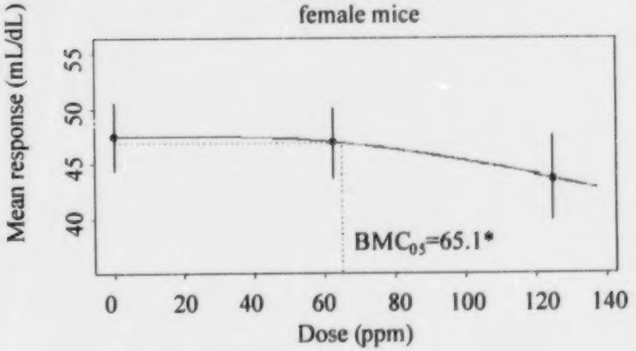
[1] Highest dose group excluded to eliminate downturn from dose–response relationship.

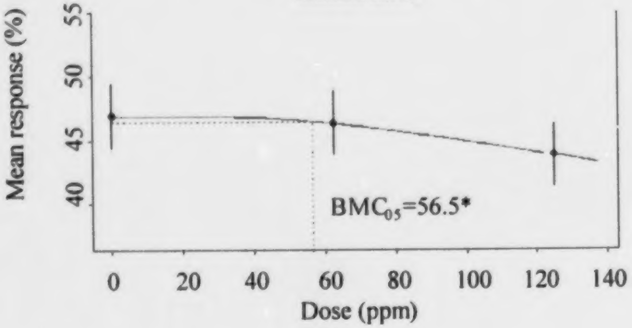
Figure 1: Exposure–response curves for hematological effects in mice and rats

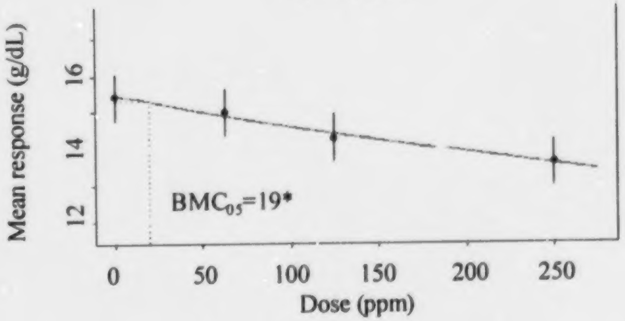


* BMC_{05} unadjusted for non-constant dosing

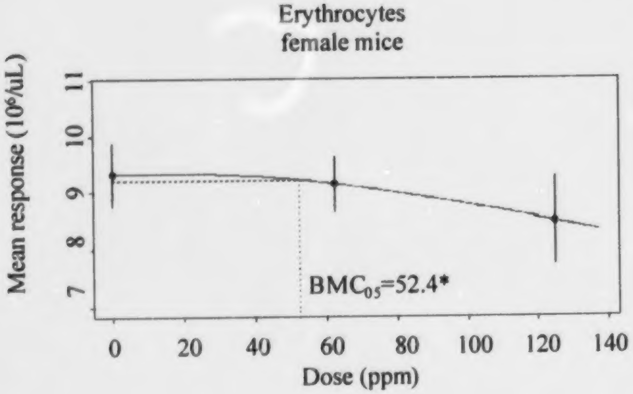

Platelets
male mice

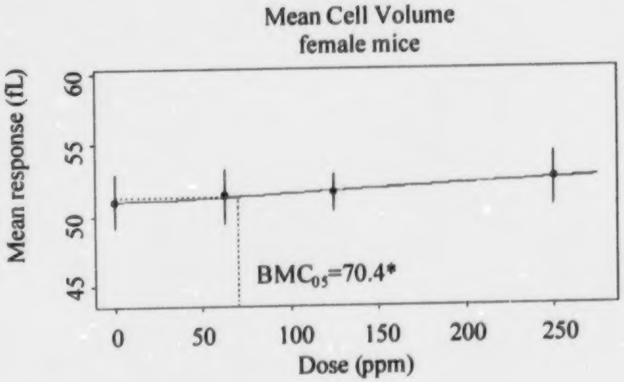

Automated Hematocrit
female mice

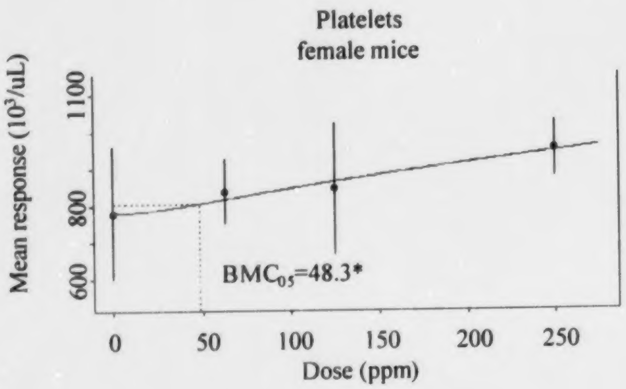

Manual Hematocrit
female mice

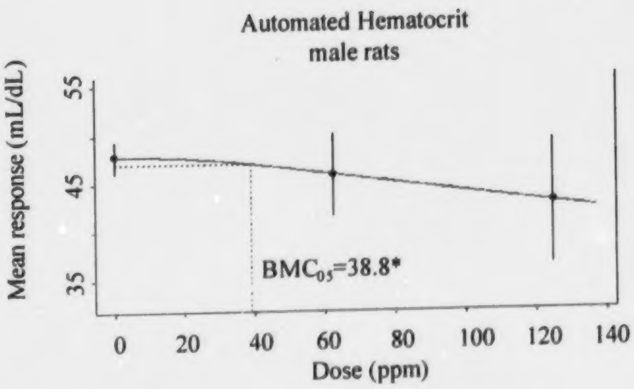

Hemoglobin
female mice

* BMC_{05} unadjusted for non-constant dosing


Erythrocytes
female mice

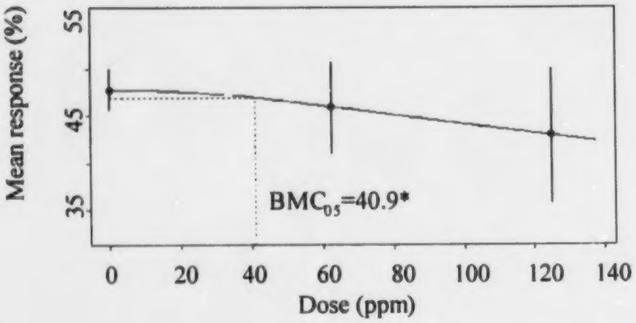

Mean Cell Volume
female mice


Platelets
female mice

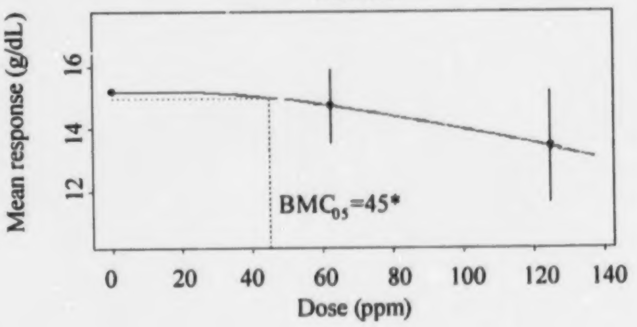

Automated Hematocrit
male rats

* BMC$_{05}$ unadjusted for non-constant dosing

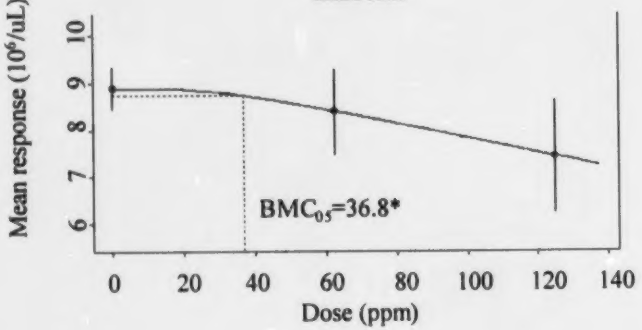
Manual Hematocrit
male rats



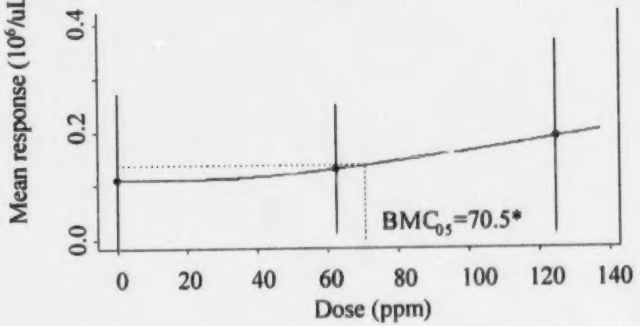
Hemogobin
male rats



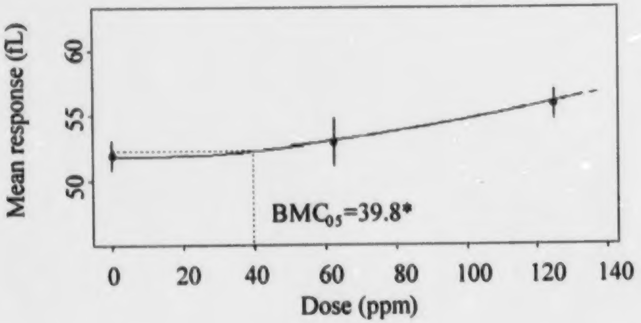
Erythrocytes
male rats



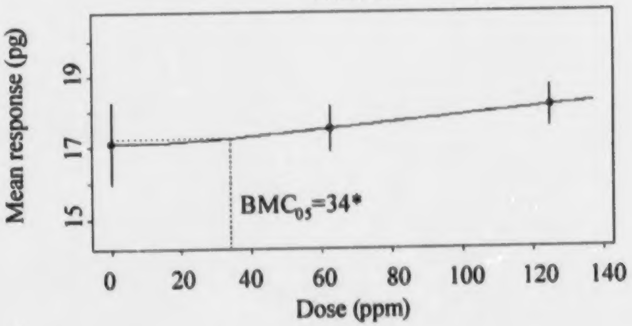
Reticulocytes
male rats



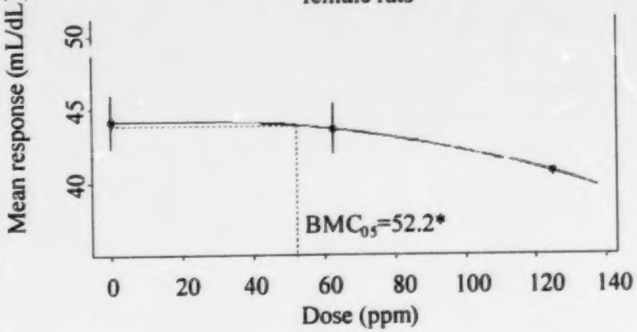
* BMC$_{05}$ unadjusted for non-constant dosing



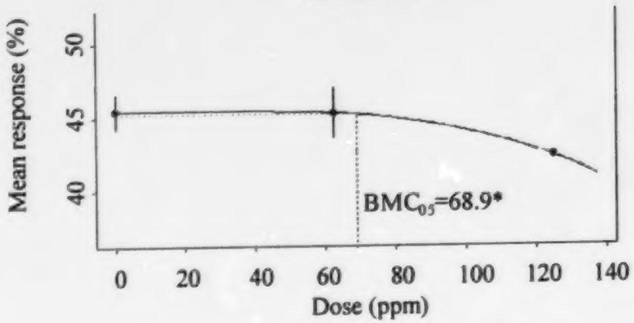
Mean Cell Volume
male rats



Mean Cell Hemoglobin
male rats

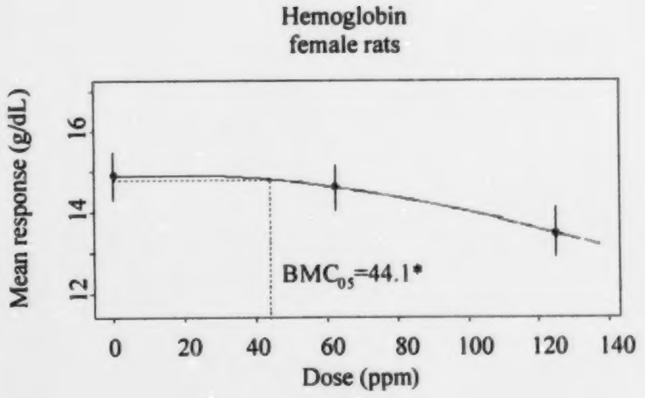


Automated Hematocrit
female rats

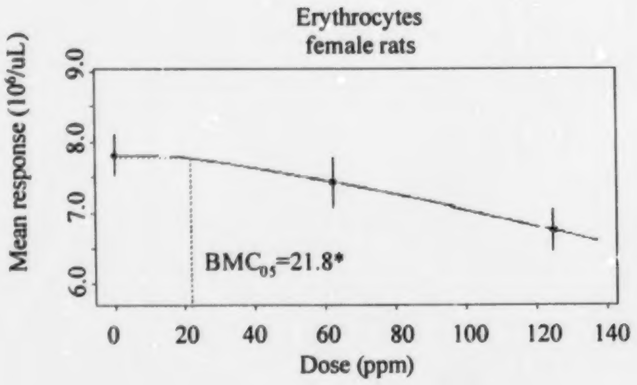


Manual Hematocrit
female rats

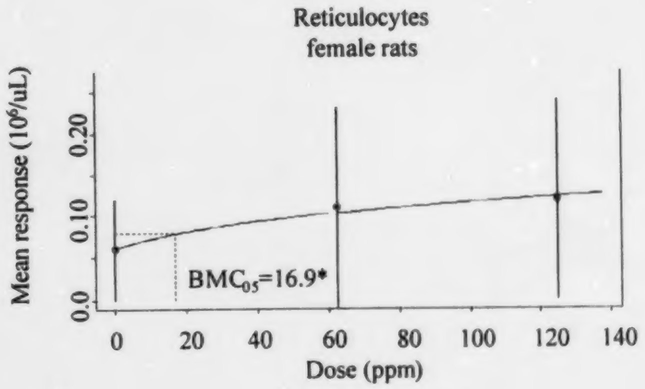
* BMC$_{05}$ unadjusted for non-constant dosing



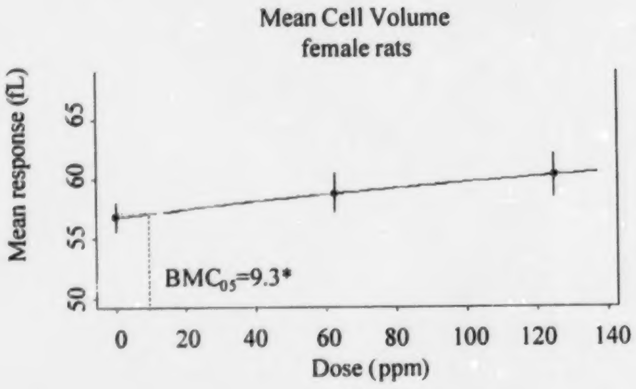
Hemoglobin
female rats



Erythrocytes
female rats

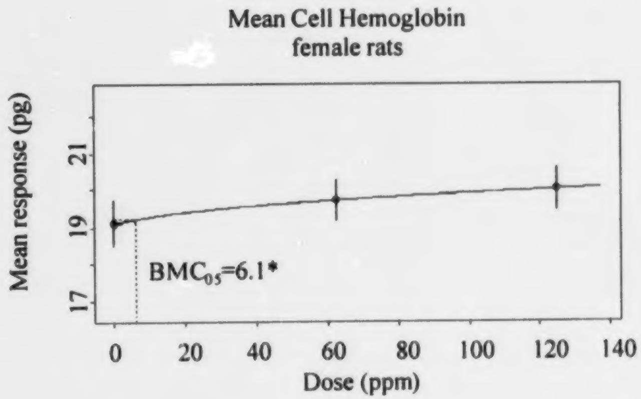


Reticulocytes
female rats



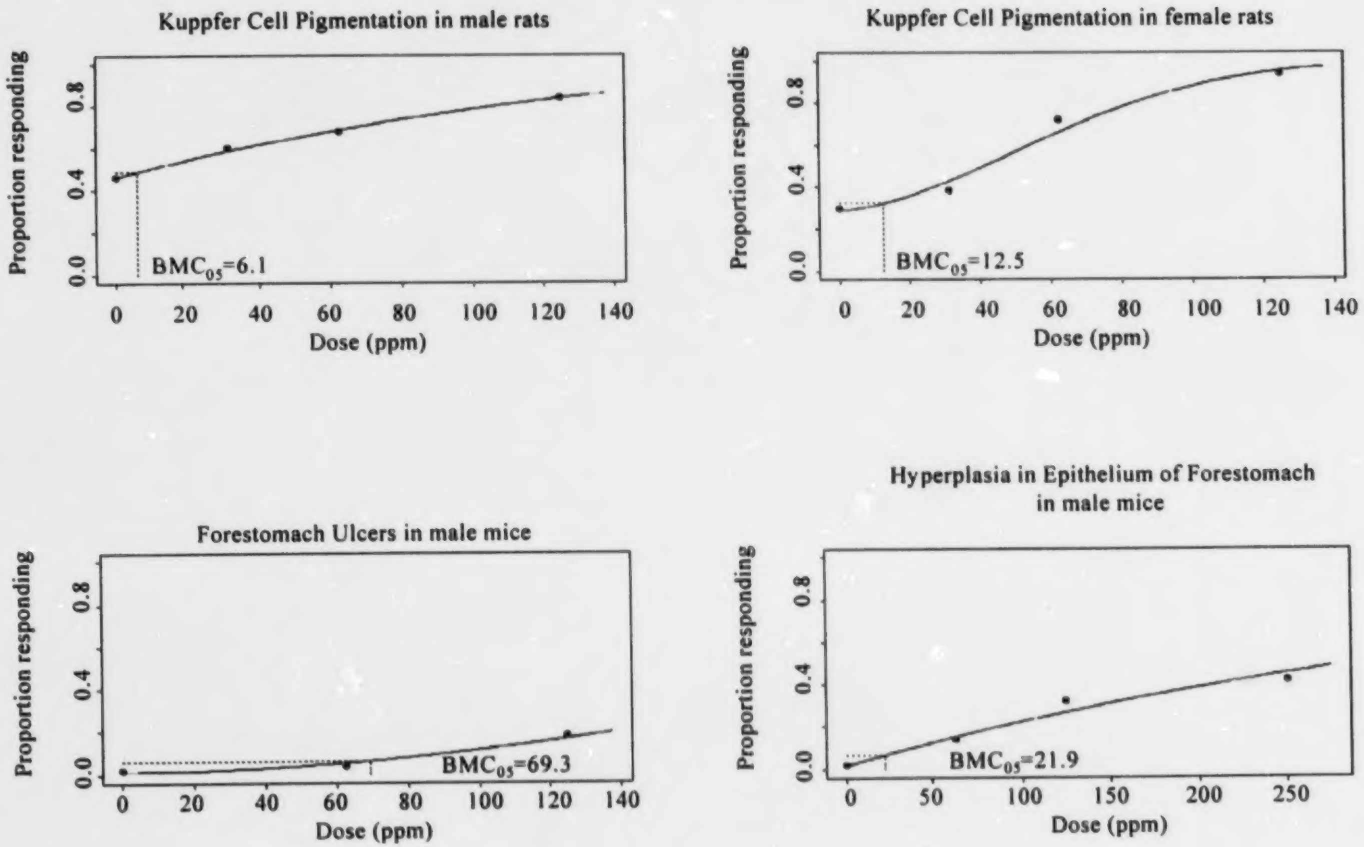
Mean Cell Volume
female rats

* BMC$_{05}$ unadjusted for non-constant dosing


Mean Cell Hemoglobin
female rats

* BMC$_{05}$ unadjusted for non-constant dosing

Figure 2: Exposure-response curves for non-haematological effects in mice and rats



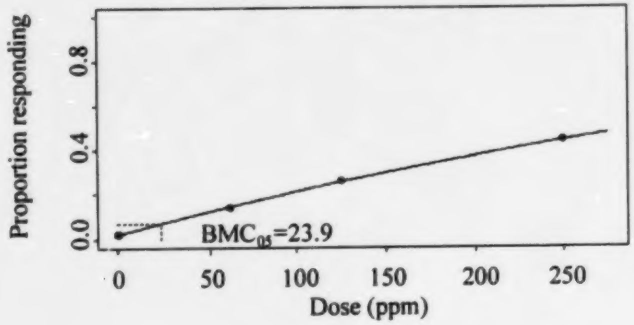
Kuppfer Cell Pigmentation in male rats

Kuppfer Cell Pigmentation in female rats

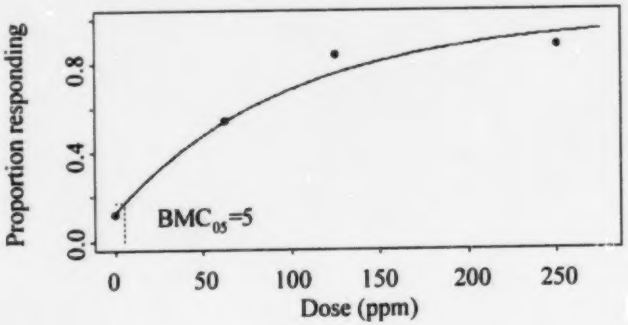
Forestomach Ulcers in male mice

Hyperplasia in Epithelium of Forestomach in male mice

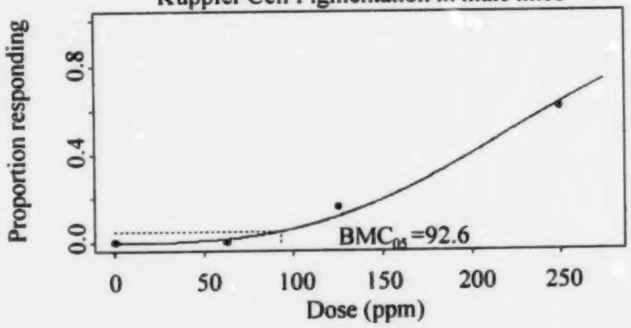
*BMC_{05} unadjusted for non-constant dosing



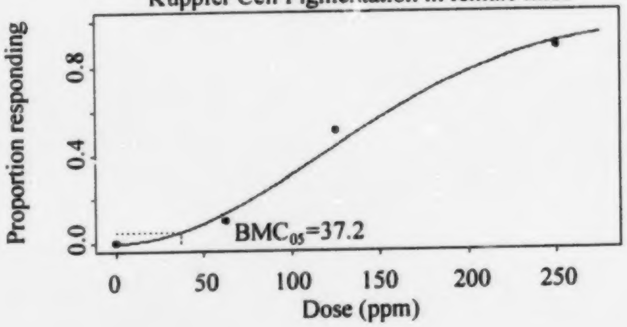
Forestomach Ulcers in female mice



Hyperplasia in Epithelium of Forestomach in female mice



Kuppfer Cell Pigmentation in male mice



Kuppfer Cell Pigmentation in female mice

* BMC$_{05}$ unadjusted for non-constant dosing

APPENDIX A: Search strategies employed for identification of relevant data

Environmental assessment

Data relevant to the assessment of whether 2-butoxyethanol is "toxic" to the environment under CEPA 1999 were identified from existing review documents, published reference texts and on-line searches, conducted between January and May 1996, of the following databases: ASFA (Aquatic Sciences and Fisheries Abstracts, Cambridge Scientific Abstracts; 1990–1996), BIOSIS (Biosciences Information Services; 1990–1996), CAB (Commonwealth Agriculture Bureaux; 1990–1996), CESARS (Chemical Evaluation Search and Retrieval System, Ontario Ministry of the Environment and Michigan Department of Natural Resources; 1996), CHRIS (Chemical Hazard Release Information System; 1964–1985), Current Contents (Institute for Scientific Information; 1993, 1994, 1995, up to January 15, 1996), ELIAS (Environmental Library Integrated Automated System, Environment Canada library; January 1996), Enviroline (R.R. Bowker Publishing Co.; November 1995 – June 1996), Environmental Abstracts (1975 – February 1996), Environmental Bibliography (Environmental Studies Institute, International Academy at Santa Barbara; 1990–1996), GEOREF (Geo Reference Information System, American Geological Institute; 1990–1996), HSDB (Hazardous Substances Data Bank, U.S. National Library of Medicine; 1996), Life Sciences (Cambridge Scientific Abstracts; 1990–1996), NTIS (National Technical Information Service, U.S. Department of Commerce; 1990–1996), Pollution Abstracts (Cambridge Scientific Abstracts, U.S. National Library of Medicine; 1990–1996), POLTOX (Cambridge Scientific Abstracts, U.S. National Library of Medicine; 1990–1995), RTECS (Registry of Toxic Effects of Chemical Substances, U.S. National Institute for Occupational Safety and Health; 1996), Toxline (U.S. National Library of Medicine; 1990–1996), TRI93 (Toxic Chemical Release Inventory, U.S. Environmental Protection Agency, Office of Toxic Substances; 1993), USEPA-ASTER (Assessment Tools for the Evaluation of Risk, U.S. Environmental Protection Agency; up to December 21, 1994), WASTEINFO (Waste Management Information Bureau of the American Energy Agency; 1973 – September 1995) and Water Resources Abstracts (U.S. Geological Survey, U.S. Department of the Interior; 1990–1996). Reveal Alert was used to maintain an ongoing record of the current scientific literature pertaining to the potential environmental effects of 2-butoxyethanol. Data obtained after September 30, 1999, were not considered in this assessment.

In addition, a survey of Canadian industry was carried out under the authority of Section 16 of CEPA (Environment Canada, 1997b,c). Targeted companies with commercial activities involving more than 1000 kg of 2-butoxyethanol were required to supply information on uses, releases, environmental concentrations, effects or other data that were available to them for 2-butoxyethanol.

Health assessment

In addition to studies included in the review prepared by BIBRA Toxicology International and relevant studies included in reports published by the International Programme on Chemical Safety (IPCS, 1998) and the Agency for Toxic Substances and Disease Registry (ATSDR, 1998), recent data have been identified through searching the following databases beginning in August of 1996 using the chemical name or the CAS number for both 2-butoxyethanol and 2-butoxyethyl acetate: Canadian Research Index, DIALOG (Cancerlit, Environmental Bibliography, Waternet, Water Resources Abstracts, Enviroline, CAB Abstracts, Food Science and Technology Abstracts, Pollution Abstracts and NTIS), Medline, Toxline Plus and TOXNET (CCRIS [Chemical Carcinogenesis Research Information System, U.S. National Cancer Institute], GENE-TOX [Genetic Toxicology, U.S. Environmental Protection Agency] and EMIC [Environmental Mutagen Information Center database, Oak Ridge National Laboratory]). Data acquired as of October 1999 were considered for inclusion in this report.

As well as these databases, officials at the Product Safety Bureau and Drugs Directorate of Health Canada, along with the Pest Management Regulatory Agency, were contacted to obtain information relevant to this assessment.